CONTENTS OF VOLUME XIX

No. 1. February 1956

		Page
Cryptic Arteriovenous and Venous Hamartomas of the Brain	J. V. Crawford and Dorothy S. Russell	1
The Action of the Phosphatases of Human Brain on Lipid Phosphate Esters	K. P. Strickland, R. H. S. Thompson, and G. R. Webster	12
The Effect of the Duration of Vitamin-A Deficiency in Female Rabbits Upon the Incidence of Hydrocephalus in their Young	J. W. Millen and D. H. M. Woollam	17
A Clinical Correlation between Encephalopathy and Papilloedema in Addison's Disease	Antony Jefferson	21
Benign Intracranial Hypertension	Peter Bradshaw	28
Hyperostosis Frontalis Interna	S. Smith and R. E. Hemphill	42
A Family with the Progressive Hypertrophic Polyneuritis of Dejerine and Sottas	P. D. Bedford and F. E. James	46
Growth of the Skull in Young Children: Part I: Standards of Head Circumference	C. K. Westropp and C. R. Barber	52
Part II: Changes in Head Shape	C. R. Barber and D. Hewitt	54
Altered Response to Small Doses of Insulin Associated with Electroplexy and Hypoglycaemic Therapies	E. Marley	57
The Value of the Marchi Method for Staining Tissue Stored in Formalin for Prolonged Periods	Marion C. Smith, Sabina J. Strich, and Peter Sharp	62
Book Reviews		65

No. 2. May 1956

		Page
Observations on the Extended Use of the Marchi Method	Marion C. Smith	67
The Recognition and Prevention of Artefacts of the Marchi Method	Marion C. Smith	74
Studies in Sensation: Observations on the Localization of the Sensations of Touch and Prick	John Marshall	84
Reference of Sensation at the Spinal Level	P. W. Nathan	88
Awareness of Bladder Filling with Divided Sensory Tract	P. W. Nathan	101
Two Cases of Myopathy Limited to the Quadriceps	John N. Walton	106
A Study of 25 Cases of Compression of the Cauda Equina by Prolapsed Intervertebral Discs	W. Bryan Jennett	109
E.E.G. Abnormalities from the Temporal Lobe Studied with Sphenoidal Electrodes	G. Pampiglione and J. Kerridge	117
The Effect of Insulin Coma and E.C.T. on the Short-term Prognosis of Schizophrenia	J. Hoenig, D. M. Leiberman, and I. Auerbach	130
Sodium Amytal and Behaviour in Neurotic Subjects	S. G. Laverty and C. M. Franks	137

Page

Disseminated Sclerosis Treated with Isoniazid with a Method of Evaluating Chronic Neurological Disorders
Barbara M. Ansell and Edwin Clarke 144

Ischaemic and Post-ischaemic Paraesthesiae: Normal Responses in the Upper Limb with Special Reference to the Effect of Age E. W. Poole 148

Familial Peroneal Muscular Atrophy and Its Association with the Familial Ataxias and Tremor and Longevity Raymond Hierons 155

Book Reviews 161

No. 3. August 1956

Page

Diffuse Degeneration of the Cerebral White Matter in Severe Dementia Following Head Injury Sabina J. Strich 163

Retinal Degeneration in Hereditary Ataxia
Å. Björk, U. Lindblom, and L. Wadensten 186

Paroxysmal Dysphasia and the Problem of Cerebral Dominance
H. Hécaen and Malcolm Piercy 194

The Prolonged and Distant Effects of Experimental Brain Injury on Cerebral Blood Vessels as Demonstrated by Radioactive Indicators
James B. Brierley 202

Multilocular Encephalomalacia W. Kramer 209

The Pathological Effects of Cerebral Arteriography T. Crawford 217

Electrophoresis of Sera in Multiple Sclerosis and Other Neurological Diseases Elizabeth M. Press 222

Benign Congenital Myopathy with Myasthenic Features
John N. Walton, Norman Geschwind, and J. A. Simpson 224

A Controlled Clinical Study of Chlorpromazine and Reserpine in Chronic Schizophrenia Michael Shepherd and David C. Watt 232

Book Reviews 236

No. 4. November 1956

Page

Pearly Tumours in Relation to the Central Nervous System
John S. Tytus and Joe Pennybacker 241

Physiological Tremor John Marshall and Geoffrey Walsh 260

Subacute Myoclonic Spinal Neuronitis
A. M. G. Campell and Hugh Garland 268

Electrical Signs in the Diagnosis of Carpal Tunnel and Related Syndromes John A. Simpson 275

Ischaemic and Postischaemic Paraesthesiae in Polyneuritis E. W. Poole 281

The Pupillary Changes in the Holmes-Adie Syndrome G. F. M. Russell 289

Sensory Deficits in Visual Agnosia G. Ettlinger 297

Inappropriate Affect Arthur Harris and Maryse Metcalfe 308

Book Reviews 314

Index to Volume 19 318

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 1.

CRYPTIC ARTERIOVENOUS AND VENOUS HAMARTOMAS OF THE BRAIN

BY

J. V. CRAWFORD and DOROTHY S. RUSSELL

From the Neurosurgical Department and Bernhard Baron Institute of Pathology, The London Hospital

In any large series of cases of spontaneous cerebral haemorrhage there are some of obscure aetiology that have certain clinical features in common. They occur in the younger age-groups, and although the onset of symptoms may be sudden, loss of consciousness is often delayed or incomplete. The cause of the bleeding often remains obscure on clinical examination and full investigation. Before the catastrophe the patient's condition has given no hint of any latent cerebral lesion. Although ultimate anatomical examination may reveal a vascular anomaly, the responsible lesion may be difficult to locate both on account of its situation and small size. For these reasons we propose the name " cryptic " for the series to be described. The incidence of these cryptic hamartomas in a total necropsy series of 461 examples of spontaneous intracranial haemorrhage, with a brief morphological account, has been published by one of us (Russell, 1954).

MATERIAL

This series comprises a total of 20 cases derived both from the Neurosurgical Department (seven with survival after operation) and the necropsy records (13) of the London Hospital. All were under 40 years of age, 15 being under 20 years. The sex distribution is 11 males to nine females.

The cases are divided into three groups according to the anatomical situation of the lesion : Group I, related to the cerebral convexities ; Group II, central cerebral ; and Group III, cerebellar.

GROUP I

This group comprises 10 cases, six of which came to necropsy (Table 1). A fuller account of Cases 6, 8, and 9 is given below for illustrative purposes.

Clinical Summary

As a rule the neurological disturbance comes without warning, usually during the daytime. The subject, having been perfectly well, collapses at school or in the street, or in other unprovocative circumstances. Complaint of intense headache is accompanied by vomiting and shock. Convulsions sometimes occur. The pupils are often inactive and there may be a strabismus. Flaccidity of the limbs is followed by spasticity on one or both sides of the body, with extensor plantar responses. Involuntary movements of the limbs may occur in association with intraventricular haemorrhage. At a varying interval drowsiness deepens to coma, with cyanosis, stertorous breathing, and a full, bounding pulse. In the fatal cases, deeply bloodstained fluid is often obtained by lumbar puncture, because of the frequency of ventricular haemorrhage. In these cases death has followed within a few hours or days of the onset.

Pathology

In all but two examples in this series, the lesion was in the area of supply of the middle cerebral artery ; one each lay in the areas of the anterior and posterior arteries respectively. The left hemisphere was affected in six, the right in four cases. On inspection the lesion sometimes appeared on the surface (Case 9 ; Fig. 1) as a small cluster of

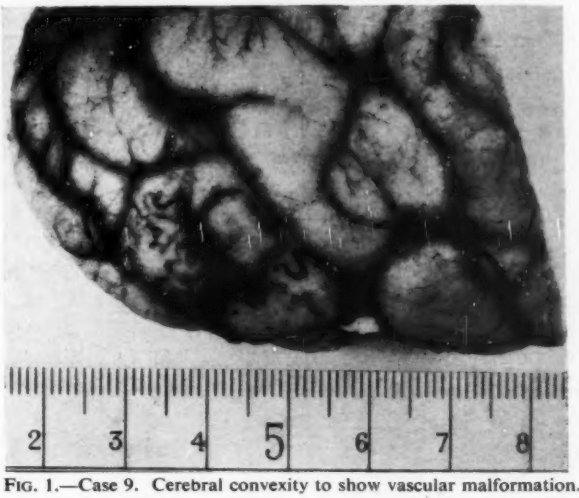


FIG. 1.—Case 9. Cerebral convexity to show vascular malformation.

TABLE I

GROUP I

Series No.	Age	Sex	Territory	Duration of Symptoms	Main Clinical Features	Operative/Necropsy Findings
1	3	F	R. mid. cerebral	12 hours. Fatal	Sudden collapse. L.-sided convulsions. Died in status epilepticus	Tortuous enlarged veins upper parietal region. Underlying haematoma 7×6×3 cm. Ventricular and slight subarachnoid haemorrhage. *Microscopy:* arteriovenous hamartoma penetrating cortex
2	15	M	L. mid. cerebral	2 hours. Fatal	Collapsed in street. Admitted moribund. Died on way to ward	Haematoma 10×2×2 cm. in centrum semiovale. Ventricular haemorrhage. No vascular lesion seen. *Microscopy:* structural changes (arteries) in depths of Sylvian fissure; suggestive but not conclusive
3	16	F	R. mid. cerebral	7 hours. Fatal	Sudden collapse. Vomiting. Coma. Clonic spasms. Absent reflexes. Steady deterioration	Arteriovenous malformation 3×0·5 cm. over ascending parietal. Ventricular haemorrhage. *Microscopy:* arteriovenous hamartoma penetrating cortex to white matter
4	24	F	L. mid. cerebral	2 weeks. Survived	Onset severe headaches. A week later mild dysphasia. O.E. papilloedema and mild R. hemiparesis with sensory loss. Clinically regarded as glioma. Ventriculography: a L.-sided haematoma encountered. Craniotomy performed	Temporo-parietal haematoma evacuated. Leash of abnormal vessels seen. *Biopsy:* abnormal vein in cortex; otherwise granulation tissue and gliosis only. Known to be well 4 years later
5	32	F	L. post cerebral	4 days. Fatal	8 months pregnant. Sudden collapse. Remained semi-comatose, fixed pupils and R. hemiplegia. Gradually deepened into coma. L. sub-temporal decompression performed, but she continued to deteriorate	Arteriovenous malformation 1·2×0·7 cm. ventral occipital. Haematoma 10×3·5×2 cm. temporo-occipital. Subarachnoid and subdural haemorrhage. *Microscopy:* arteriovenous hamartoma (Fig. 3)
6	12	M	L. ant. cerebral	3 episodes in 3 years. Fatal haemorrhage	See case report	See case report
7	32	M	L. mid. cerebral	2 episodes 4 years apart. Survived	1947 L. cerebral haemorrhage. Symptoms subsided spontaneously over weeks. 1951 recurrence with dysphasia, hemiparesis, and hemianopia. Angiogram confirmed L. temporo-parietal mass; no abnormal vessels seen	Temporo-parietal haematoma evacuated. Leash of abnormal vessels seen in medial wall of haematoma adjacent to ventricle. *Biopsy:* enlarged tortuous arteries and veins in adjacent pia. Known to be well
8	16	F	R. mid. cerebral	6 weeks. Survived	See case report	See case report
9	8	M	R. mid. cerebral	12 hours. Fatal	See case report	See case report
10	11	F	L. mid. cerebral	8 days. Survived	Sudden onset intense headache lapsing into semi-coma. Remained stationary. O.E. aphasic, papilloedema, R. hemiparesis with movements of R. arm. Arteriogram suggests L. parietal mass, no abnormal vessels. Ventriculogram haematoma-cavity entered on L. Craniotomy performed	Temporo-parietal haematoma exposed and evacuated. Leash of abnormal vessels seen in the antero-medial wall of the cavity adjacent to the ventricle. No biopsy. Known to be well

tortuous and dilated vessels related to the underlying haematoma. But sometimes it was buried in the depths of a sulcus while the surface vessels appeared quite normal (Case 6; Fig. 2). It is indeed likely, as perhaps in Case 2, that certain of these deeper lesions are destroyed in the event of a large haemorrhage. We have in our own necropsy records certain other cases, excluded from this study, in young subjects in whom the source of a large spontaneous haemorrhage has not been demonstrated. The frequent absence of any enlargement and tortuosity of the vessels upon the adjacent surface of the brain is an important reason why their demonstration is, in any event, apt to be difficult.

The size of the haematoma has varied considerably. In our necropsies the smallest measured 3 by 0·5 cm.; the largest 10 by 3·5 by 2 cm. But in four of these six cases the ventricular system was also involved. In addition to leptomeningeal haemorrhage, subdural haemorrhage occurred in Cases 5 and 6; the latter was doubtless due to rupture of the arachnoid membrane under pressure.

Microscopically, these vascular hamartomas are composed of enlarged and tortuous arteries and veins occupying a restricted area of the pia and subjacent cerebrum in the region of the haemorrhage (Figs. 2, 3). As in the better known larger lesions, the intima and media are structurally abnormal, the muscular and elastic elements displaying a hap-

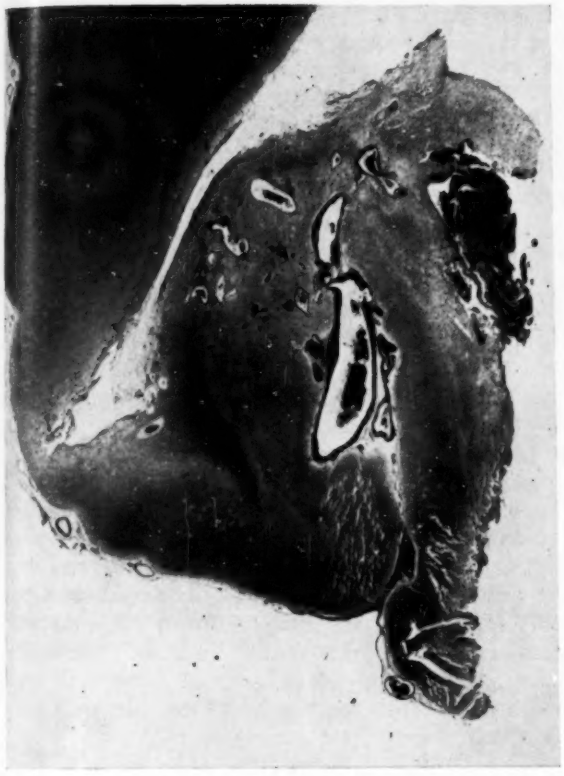


FIG. 2.—Case 6. Coronal section through gyrus rectus (left) containing cavity, and border of recent haemorrhage (right). Between these, and in depths of sulcus, tissue occupied by arteriovenous hamartoma. Haematoxylin and eosin. × 3 approx.

FIG. 3.—Case 5. Temporo-occipital cortex in border of haematoma showing malformed vessels in meninges and cortex. Phosphotungstic-acid haematoxylin. × 7.

hazard hyper- or hypoplasia. The intima is often thickened by cushions of fibromuscular tissue. Fibrous thickening of a more diffuse character usually affects the veins.

Variable amounts of fibrillary gliosis are found in the intervening neural tissues and, occasionally, foci of macrophages containing haemosiderin representing previous leakages of blood.

Illustrative Cases

Case 6 (Neurosurg. No. 5960/49).—A boy, age 12, was admitted on June 8, 1949.

Clinical History.—Three years before admission to the London Hospital he had an episode of intense headache and neck stiffness which lasted two days. Three months ago he had another attack of headache and was admitted to a local hospital. Lumbar puncture yielded bloodstained cerebrospinal fluid. He rapidly improved and was free of symptoms at the time of his admission for investigation. Examination revealed no abnormal physical signs. He was right-handed. On June 13, carotid angiography was performed under general anaesthesia. The *x*-ray pictures showed in one projection an abnormal collection of fine vessels in the left frontal region (Fig. 4). Following this procedure he remained unconscious for some hours and was then found to be aphasic and to have a right hemiplegia. He improved steadily. Two weeks later he was making only occasional mistakes in his speech, his right leg was

FIG. 4.—Case 6. Angiogram to show vascular abnormality (arrow).

normal, but his right hand remained clumsy and weak. A course of deep *x* rays was given to the left frontal angioma. On July 21, a few hours before going home, he suddenly developed intense headache, became aphasic, and started having right-sided convulsions. He passed into coma and died within an hour of this.

Pathology.—Necropsy (P.M. 263/49) was limited to examination of the brain. An interrupted layer of recent blood clot occupied the subdural space over the cerebral hemispheres, the left side being mainly affected. The left frontal pole was expanded by similar clot, part of which escaped during removal of the brain. There was orange pigmentation of the leptomeninges over the left gyrus rectus and adjacent medial surface of the frontal pole. No visible abnormality was found on dissection of the circle of Willis and the main cerebral arteries, the left middle and anterior cerebral vessels being fully dissected. The main dural venous sinuses contained fluid blood. The left common carotid artery showed two puncture wounds 2·5 cm. below its bifurcation but was otherwise macroscopically and microscopically normal. On coronal section of the fixed brain, the white matter of the left frontal lobe contained two cavities of about equal size. The more medial, measuring 5 cm. dorsiventrally by 1 cm. from side to side and 4·5 cm. from before back, extended into the subcortical white matter of the gyrus rectus and posteriorly almost reached the ependyma of the frontal horn. Its walls were smooth and glistening, with patches of *café-au-lait* staining; a few filaments and membranes of soft grey tissue traversed the space. The more lateral cavity was separated from the medial one by a partition of white matter 0·5 cm. thick. Its walls were of soft, ragged white matter containing a few fragments of recent clot (Fig. 2).

Apart from these cavities an old friable infarct occupied the cortex of the left middle frontal convolution, extending from the coronal level of the genu of the corpus callosum to involve the inferior frontal convolution, the adjacent operculum, and part of the corona radiata. Similar infarction affected a large area of the parieto-occipital cortex, ending 3 cm. in front of the occipital pole. There was considerable pultaceous softening of the subcortical white matter in the occipital lobe. The rest of the brain appeared normal.

Microscopic Examination.—Although unseen macroscopically, two of the four sections taken through the cavities in the frontal pole reveal an arteriovenous malformation related to both (Fig. 2). It occupies the cortex and subcortical white matter of the inferior aspect of the lobe in the depths of a sulcus, and is supplied by abnormally large, malformed vessels in the leptomeninges. The enlarged and tortuous elements of this lesion are individually separated by neural tissues in which there is considerable focal gliosis. One of the vessels is partly occluded by recent thrombus and there is recent haemorrhage in its immediate neighbourhood.

The medial cavity extends into the cortex; it is lined with a thin layer of organized granulation tissue containing small lymphocytes and many pigmented macrophages. The walls of the lateral cavity are composed of ragged oedematous cortex and white matter containing small recent haemorrhages. Sections from the infarcted areas in the posterior frontal and parietal lobes confirm the macroscopic appearances of old anaemic infarcts. None of the meningeal arteries bears evidence of previous occlusion, but the adventitia of a small artery in the parietal region contains a small group of foreign-body giant cells.

The medial cavity in the frontal pole represents the site of an old haemorrhage corresponding either to the initial disturbance recorded three years ago, or to the more recent incident three months ago. From evidence published elsewhere (Russell, 1954) the more recent of these dates may be excluded. The pigmentation of the adjacent leptomeninges testifies to its leakage in the region of the gyrus rectus. The lateral cavity is obviously the result of a terminal haemorrhage. This also gave way into the leptomeninges and, presumably from sudden focal pressure, into the subdural space.

The pathological examination does not establish the origin of the infarcts in the hinder part of the left cerebrum. But the group of foreign-body giant cells in the adventitia of one meningeal artery suggests the escape there of some substance which excited this reaction and that substance may have been the diodone used in angiography.

Case 8 (L.H. No. 34458/51).—A girl, aged 16, was admitted on September 16, 1951.

Clinical History.—For six weeks before admission she suffered frequent bifrontal headache, often severe enough to stop her from working. She had never before had headaches. One night, three weeks ago, she awoke feeling sick and could not use her limbs properly. She became semiconscious. On admission to a local hospital neck rigidity and a left hemiplegia were noted. Lumbar puncture yielded heavily bloodstained fluid. During the first week in hospital her level of consciousness gradually improved. On transfer to The London Hospital she was alert and orientated. There was moderate neck stiffness and positive Kernig's sign. The fundi were normal. She had a complete flaccid left hemiplegia with analgesia, hypoaesthesia, and postural loss on the left. Plantar responses were ↓ ↑. On September 19, right carotid angiography showed a very small irregular vascular malformation in the parietal region with evidence of an adjacent intracerebral mass (Fig. 5). On September 25, a right lateral osteoplastic flap was raised and a centro-parietal intracerebral haematoma evacuated. In the posterior wall of the haematoma there was a small knot of blood vessels, a few millimetres wide, going down into a tougher piece of clot. This was removed for histological study. Vessels were then encountered passing through a thin septum between the cavity and the lateral ventricle. These were coagulated. Her post-operative course was uneventful. A post-operative angiogram (on October 5) showed the small hamartoma to have been removed (Fig. 6). At the time of her discharge (November 13) there was still

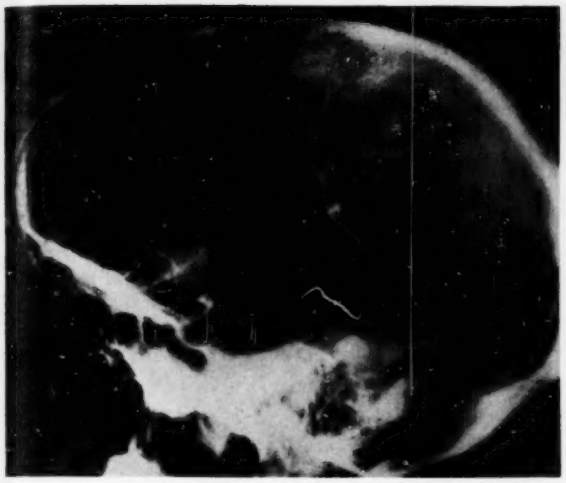


FIG. 5.—Case 8. Angiogram to show vascular abnormality before operation (arrow).

considerable residual weakness of the left face, arm, and leg. She was able to walk when fitted with a toe-spring. Some sensory loss also persisted on the left. She has been seen at regular intervals and still shows a severe left spastic hemiparesis, most apparent in the hand. She is able to do most housework, however, and walks quite well with a lateral iron.

Pathology.—Small fragments of recent clot, granulation tissue, cerebral cortex, and white matter were received. In the latter there are several greatly enlarged vessels with stout collagenous walls and no elastic tissue, which are probably altered veins. In the few arteries identified there is some reduplication of the internal elastic lamella, but they are not otherwise abnormal. Abundant foam cells, often containing granules of iron-pigment, occupy the granulation tissue.

Case 9 (L.H. No. 2628/54).—A boy, aged 8, was admitted on January 25, 1954.

FIG. 6.—Case 8. Angiogram following operation. A silver clip indicates neighbourhood of extirpated lesion.

FIG. 7.—Case 9. Subcortical anomalous vessels below focus shown in Fig. 1. Phosphotungstic-acid haematoxylin. × 9.

Clinical History.—About eight hours before admission he received a slight blow on the back of the neck ; five hours later he returned from school with intense headache and vomiting. He gradually lost consciousness and by the time of his admission he was in coma. There were frequent jerking movements of all the limbs and frothing at the mouth, and occasional episodes of Cheyne-Stokes respiration. He had marked neck stiffness ; the pupils were dilated and fixed, and the corneal reflexes were absent. Both plantar responses were extensor. Biparietal and bitemporal burr-holes were made to exclude surface haematoma. Heavily bloodstained fluid was found in both lateral ventricles. His condition became desperate and he died three hours later (12 hours after the onset of symptoms).

Pathology.—No abnormalities were observed at necropsy (P.M. 29/54) apart from the brain. The cerebral hemispheres were moderately flattened. All the main cerebral arteries appeared normal and symmetrical. The right occipital lobe was expanded by a haematoma, measuring 3 by 1·5 cm., which occupied the white matter between the ventricle and the junction of the right superior and inferior parietal lobules posteriorly ; it had ruptured into the ventricle. On the adjacent surface of the brain, the leptomeninges contained a cluster of dilated blood vessels measuring about 1·5 cm. diameter (Fig. 1). Immediately beneath this and

abutting on the haematoma, a group of vessels with thickened walls was visible under magnification, the patch so occupied measuring less than 1 cm. Further examination of the brain revealed haemorrhage throughout the ventricular system. There was no abnormality in the cervical spine and cord.

Microscopic Examination.—The subcortical focus is composed of enlarged, tortuous, malformed vessels (Fig. 7). Most of these are veins with thickened collagenous walls containing scanty and irregularly distributed muscle fibres. A few arteries in the area are enlarged with abnormally developed elastica. In the tissue between the vessels there is patchy gliosis, severe focal oedema, and recent haemorrhage. Near the ventricle there is free iron-pigment in macrophages adjacent to some of the vessels, and an ill-defined group of foam cells. It is evident from this that slight leakage of blood had taken place at some antecedent period.

GROUP II

The four cases in which a central cerebral arteriovenous malformation was demonstrated all came to necropsy (Table II).

Clinical Summary

The resemblance between these and the rapidly fatal examples of Group I is close. The onset was similarly dramatic with progression into deep coma followed by death within a few hours, or on the following day. The clinical data available are scanty and provide no distinctive features by which the site of the haemorrhage could be identified. From the nature and location of the lesions in this group it is most unlikely that any form of active treatment could avail.

Pathology

To the naked eye these lesions were either entirely or predominantly venous, involving to a variable extent the tributaries of one of the lesser veins of Galen, and, in the grosser examples, the latter as well. Thus in Case 14 the right lesser vein of Galen was dilated together with its tributaries, the latter being distinctly tortuous. Many slightly dilated vessels were observed, on section, in the pulvinar. Plexiform dilatation of some arteries was found in the meninges between the right crus and the adjacent hippocampus. Death was due to massive intraventricular haemorrhage together with a small haematoma in the substance of the right optic thalamus. Microscopically the right thalamus, and in particular the pulvinar, is riddled with dilated and tortuous arteries and veins; the adjacent choroid plexus is similarly affected (Figs. 8 and 9).

In view of the anatomical situation of these vascular anomalies a large and fatal intraventricular haemorrhage is apt to be the outcome. On the other hand, the lesion, like those described in Group I, may be small and difficult to demonstrate. In such the haemorrhage may lie in the centrum semiovale, as in the example now to be described.

Illustrative Case

Case 13 (L.H. No. 31096/38).—A boy, aged 11, was admitted on July 9, 1938.

Clinical History.—Eight hours before admission he collapsed at school and became drowsy. On admission he had a flaccid paralysis of the right arm and leg. Lumbar puncture yielded clear fluid under slightly increased pressure. Overnight the child deteriorated, lapsing into coma. Slight neck rigidity was noted. The left pupil was larger than the right. The right arm and leg were now spastic. Respirations became irregular and he died 22 hours after the onset of symptoms.

Pathology.—Significant findings at necropsy (P.M. 295/38) in this case were restricted to the brain. The left cerebrum was considerably and diffusely expanded. The meninges, the main cerebral arteries and veins and their branches all appeared normal. A recent massive haematoma, measuring 8 cm. from before back by 7 cm. dorsiventrally and up to 4 cm. laterally, extended in the dorsal white matter of the left cerebrum from the anterior frontal region to the coronal level of the splenium of the corpus callosum. The external capsule and claustrum were destroyed but the basal ganglia and ependyma were intact. The walls of the cavity, after

TABLE II

GROUP II

Series No.	Age	Sex	Side	Clinical Features	Necropsy Findings
11	12	F	L	Admitted unconscious. No history available. Died in coma day after admission	Serpentine angioma of vein of corpus striatum, its tributaries, and lesser vein of Galen. Haematoma in centrum semiovale. Ventricular haemorrhage. *Microscopy:* arteriovenous hamartoma; mainly venous (Fig. 12)
12	9	M	L	"Collapsed" and admitted unconscious. Died in coma day of admission	Aneurysmal dilatation of vein of corpus striatum. Rupture. Haematoma in centrum semiovale. Ventricular haemorrhage. No microscopic preparations
13	11	M	L	See case report	See case report
14	15	F	R	"Collapsed" and brought to hospital unconscious. Died within an hour of admission	Arteriovenous hamartoma of lesser vein of Galen, its tributaries, and of arteries supplying thalamus. Small haematoma in thalamus. Ventricular haemorrhage. Diffuse subarachnoid haemorrhage (Figs. 8 and 9)

FIG. 8

FIG. 9

evacuation of the clot and fixation of the brain, were greatly softened and stippled with haemorrhages. In the corona radiata forming the medial wall, and adjacent to the head of the caudate nucleus, the white matter appeared friable and contained a few enlarged blood vessels with thickened grey walls. This area measured about 0·7 by 0·5 cm. Apparently draining from this focus was an enlarged (0·2 cm. diameter) but thin-walled vein which traversed the posterior part of the head of the caudate nucleus, beneath the ependyma, to unite with the choroid plexus close to the foramen of Monro.

Microscopic Examination.—As shown in Fig. 10, the area identified in the medial wall of the haemorrhage contains grossly abnormal vessels. Stains for elastic demonstrate the presence of arteries as well as veins, though the latter are more conspicuous in respect of enlargement and number. There can be no doubt that this malformation was responsible for the haemorrhage in view of its intimate relationship to the latter.

FIG. 8.—Case 14. Area of pulvinar occupied by grossly malformed vessels. Phosphotungstic-acid haematoxylin. × 9.

FIG. 9.—Case 14. Adjacent to Fig. 8, to show both arterial and venous elements in malformation. Verhoeff's elastic and van Gieson. × 17.

FIG. 10.—Case 13. Area containing malformed vessels in medial wall of haematoma. Masson's trichrome. × 6.

FIG. 10

FIG. 11.—Case 11. Dilated malformed vein of corpus striatum. Verhoeff's elastic. × 5 approx.

GROUP III

There are six cases in this cerebellar group; three proved rapidly fatal, while the other three were relieved by operative treatment (Table III).

Clinical Summary

The three fatal cases cannot be distinguished clinically from the similarly catastrophic examples in the preceding groups. The remaining three presented features (as exemplified by Case 20) which strongly suggested a rapidly growing cerebellar tumour. They each had a history of several weeks of increasing intracranial pressure, and developed well marked signs of cerebellar dysfunction. Indeed, the disclosure of an intracerebellar haematoma at operation in Case 19 was considered to be due to a capillary haemangioblastoma, and a search was made for a mural nodule; a suspected portion of the wall removed for microscopic examination revealed merely organizing blood clot. It was not until 15 months later, when re-exploration was necessary on account of the recurrence of symptoms, that the area containing the vascular hamartoma in the white matter of the lower vermis was found and removed. As in Group I, therefore, the distinction between the type of lesion under present consideration and a true neoplasm may only be made on occasion by operative measures.

Pathology

Although the cerebellum appears less frequently as the site of gross spontaneous haemorrhage in the vascular anomalies under discussion, it is not

TABLE III

GROUP III

Series No.	Age	Sex	Clinical Features	Site of Lesion	Pathological Findings
15	17	M	Collapsed in street. Had a fit. Brought to hospital. Died on admission	Right cerebellar lobe	Venous hamartoma. Rupture. Meningeal haemorrhage. *Microscopy:* venous hamartoma occupying white matter
16	7	M	Brought to hospital dead. No history available	Superior medullary velum	Venous hamartoma. Haemorrhage in fourth ventricle and meninges. *Microscopy:* mainly venous, also arterial hamartoma
17	11	M	Sudden onset severe headache and vomiting followed by a fit. Lost consciousness, and died in coma day of admission	Superior vermis	Haematoma in superior vermis and both lateral lobes. No vascular abnormality noted. Subarachnoid and subdural haemorrhage. *Microscopy:* arteriovenous hamartoma in deep sulcus and white matter of superior vermis
18	22	F	Four months of increasing headache. Papilloedema and nystagmus. Recorded symptom free 15 months after operation	Left cerebellar lobe	Operation—haematoma in left lobe evacuated. Large vessels in wall coagulated with diathermy. *Biopsy from wall:* granulation tissue and gliosis only
19	16	M	Two weeks increasing headache and drowsiness. Papilloedema and nystagmus. Left cerebellar haematoma evacuated. Fifteen months later recurrence and solid nodule removed at operation	Posterior vermis and left lobe	Second operation—tumour-like mass (3 cm. diameter) removed from posterior vermis. *Microscopy:* arteriovenous hamartoma
20	33	M	See case report	Left cerebellar lobe	See case report

FIG. 12.—Case 13. Small unruptured venous hamartoma in white matter of lateral lobe of cerebellum. Loyez' haematoxylin. × 12.

uncommon, in the routine macroscopic examination of sections of fixed specimens, to encounter small and clinically silent lesions of this kind without any alteration of the vessels in the adjacent leptomeninges. Such an example is illustrated in Fig. 12; it was identified as a minute pinkish-red area in the central white matter of a lateral lobe during scrutiny of the fixed brain for an unrelated neurological condition. Histologically it appears to be entirely venous. It is therefore possible that vascular hamartomas of the cerebellum are less apt to rupture than the cerebral examples. But it will be appreciated also that lesions of the dimensions illustrated may easily be so destroyed in the event of a massive haemorrhage that their subsequent identification by the pathologist is impossible. In the three fatal cases necropsy revealed considerable haemorrhage in the basal cisterns and regional leptomeninges; in one (Case 17) there was also basal subdural haemorrhage. The site of the intracerebellar haemorrhage varied: analysing all six cases a lateral lobe was alone involved in three; the vermis, with spread into one or both lateral lobes, in two; in the sixth, the haemorrhage arose from vessels in the superior medullary velum and caused extensive intraventricular haemorrhage.

Microscopically the lesion was composed of both abnormal arteries and veins in three examples (Cases 16, 17, and 19) and of veins alone in one (Case 15). In the remaining two cases the composition remains uncertain since no histological verification was obtained in one, and in the other (Case 20) the histological report (from another laboratory) neglects this point and the material is no longer available for re-examination.

Illustrative Case

Case 20 (Neurosurg. No. 910/41).—A man, aged 33, was admitted to Chase Farm Hospital on May 28, 1941.

Clinical History.—For one month he had had occipital headache and giddiness in which he "felt he was spinning to the right". He also complained of diplopia on looking to the left. Examination showed bilateral papilloedema, and sluggish pupils with coarse nystagmus on deviation to the right. There was weakness, hypotonia and ataxia of the left arm and leg. On May 30, a suboccipital craniotomy revealed broadening and flattening of the folia of the left cerebellar lobe; incision disclosed a haematoma, 3 cm. diameter, surrounded by ragged brownish membrane. There was nothing suggesting a mural nodule, but crossing the depth of the cavity was a prominent vessel resembling an artery, and there were a number of vessels in the wall of the cavity which bled very freely. Tissue from the wall of the cavity was taken for histological examination. The patient made a satisfactory recovery following this operation. At the time of his discharge (June 22) he was symptom free and nystagmus was the only residual sign. When last seen (March 27, 1942) he was free of symptoms and working steadily.

Ill-sustained nystagmus to the right was the only abnormal finding.

Biopsy.—The specimen was reported from Chase Farm Hospital as "semi-necrotic tissue containing numerous thin-walled dilated vessels, and thicker strands of collagen probably derived from larger vessels". The material is no longer available for re-examination.

DISCUSSION

Although 12 of the 20 cases in this series proved rapidly fatal, certain others (in Groups I and III) were relieved by operation. In retrospect, the lesions in Cases 5 and 6 also might have been satisfactorily removed had their true nature been appreciated at the time. But the clinical diagnosis may prove extremely difficult.

Case 8 exhibited typical features, and no diagnostic problem. She was a young person with a sudden onset of hemiplegia, but only partial impairment of consciousness, and with no previous hint of any cerebral lesion. Angiography revealed

the vascular hamartoma and intracerebral haematoma, which were then removed. The slower tempo of the neurological disturbance exemplified by Cases 4 and 10 was less typical. The history in these was thought to indicate a malignant glioma, and the true nature of the lesion was revealed when, in each, an intracerebral haematoma was tapped during ventriculography. Such occurrences emphasize the importance of attempting to establish an exact diagnosis in all such cases, even though the clinical picture may strongly suggest an inoperable lesion. For this purpose, electroencephalography, angiography, and ventriculography may all be required. Sometimes craniotomy, with a biopsy if possible, may be the only means of establishing the correct diagnosis. Moreover, the risks entailed by delay in such cases are obvious; not only may a further and fatal haemorrhage occur, as in Case 6, but a persistent serious disability may result, as in Case 8, where the transfer of the patient from another hospital was too long delayed.

Angiography showed a vascular lesion in two cases (6 and 8) of this series. In Case 6 the significance of the abnormal focus of blood vessels was controversial and no surgical intervention was undertaken. In two other cases (7 and 10) angiography was performed but no abnormal vascular filling was seen. It must be accepted that some of these cryptic vascular hamartomas are so small that they may pass undetected or even fail to fill in the angiogram. It is likely that a higher proportion will be detected by serial angiography. In the two cases in which no abnormal vessels were seen, the vascular displacement of a space-occupying lesion, i.e., a haematoma, was seen, so that the angiograms were of value. However, in Case 6, referred to above, there was no vascular displacement, and this added to the difficulty in diagnosis. We may thus regard angiography as a highly important investigation, but it is by no means conclusive in every case. Ventriculography may furnish supplementary information.

In Cases 7 and 9 there was a history of mild antecedent trauma to the head, and the diagnosis of subdural haematoma was considered. Our clinical histories do not fully establish how frequently trauma precedes cerebral haemorrhage in these cases, but it was also noted in two of four examples of vascular hamartoma reported by Margolis, Odom, Woodhall, and Bloor (1951). This factor may be relevant to the problem of *Spätapoplexie*, postulated by Bollinger in 1891. It is also of medicolegal importance, for the coroner's pathologist may misinterpret his observations in dealing with these cryptic hamartomas unless a careful scrutiny of the brain is made. In Case 5 pregnancy was probably the inciting cause of the rupture; the patient's blood pressure was normal at the time.

In Group II our data suggest that both the situation of the vascular lesion and the distribution of the haemorrhage render it improbable that any effective treatment is possible. These cases were all rapidly fatal. Sterzing (1908) recorded an example of this group, however, in a man aged 32 who survived a right hemiplegia, with speech defect, from the age of 10, and finally died from a further haemorrhage. At necropsy a collection of abnormal vessels was disclosed in the corpus striatum, extending towards the ventricle at the caudate nucleus and uniting with the vessels of the choroid plexus. As far as we are aware this is the only instance of survival from haemorrhage when the vascular anomaly has been of the Group II type.

The recognition of small venous and arteriovenous hamartomas in the cerebellum is of particular importance, first because this part of the brain is regarded as relatively immune, and secondly because their clinical recognition may lead to life-saving treatment (Cases 18 to 20). As we have already indicated the clinical distinction between these and rapidly growing cerebellar tumours, especially cystic varieties, and also abscesses, is difficult and, at operation, the finding of a haematoma may provoke the diagnosis of capillary haemangioblastoma unless the abnormal vessels are identified.

We have thought this series of cases worthy of record because the cryptic hamartomas have received little attention in the literature. Noran (1945), in a general review of the intracranial vascular tumours and malformations, recognizes that these lesions may be clinically silent and revealed only at necropsy. In illustration he quotes two cases in which the vascular anomaly (apparently venous) was discovered only on microscopy; one lay in the subcortical cerebral white matter, the other was in the cerebellum and pineal region. The most important contribution to the subject from this angle is that of Margolis and others (1951). From the post-mortem study of six cases, in four of which fatal haemorrhage was attributable to small vascular malformations, they identified three in which an arteriovenous (Case 1) or venous (Cases 3 and 4) lesion was responsible; in the first the depths of a left parietal sulcus and the adjacent brain were involved, in Case 3 it lay anterior to the right caudate nucleus, and in Case 4 a tributary of the left lesser vein of Galen was responsible. In their Case 2 the lesion was pontine and, from the description, was perhaps a cavernous

hamartoma. These authors specially mention the liability of young subjects to be affected by spontaneous haemorrhage, the sudden onset of symptoms with delayed loss of consciousness, and the occasional history of slight trauma. Approaching the problem of subcortical haematomas in non-hypertensive subjects from the surgical angle, Werner (1954) has found the pathogenesis obscure in his series of eight treated cases. Since these were all in young and middle-aged adults it is probable that some at least were of the kind we have described in Group I.

We conclude by quoting Dandy (1928) who states that it is

> "a fairly safe, but not absolute, rule that when a cerebral hemorrhage occurs during youth or middle age, *i.e.*, before the time when vascular accidents are to be expected, there must be an underlying tumor or aneurysm, either of which will contribute defective vessels".

"Aneurysm" here implies an arteriovenous malformation.

SUMMARY

Twenty cases of spontaneous cerebral and cerebellar haemorrhage in young subjects, due to small arteriovenous or venous hamartomas of the brain, are reported.

The term "cryptic" is proposed for such hamartomas on account of their latent character clinically and the pathological features.

The cases are divided into three groups on an anatomical basis: (I) related to the cerebral convexities; (II) central cerebral; (III) cerebellar.

Seven of the cases survived operation; the remaining 13 were demonstrated at necropsy.

Clinically the cases presented either as catastrophic apoplexies or, less acutely, simulating rapidly growing neoplasms.

Figs. 3 and 10 reproduced by courtesy of the Editor of *Proceedings of the Royal Society of Medicine*.

REFERENCES

Dandy, W. E. (1928). *Arch. Surg., Chicago*, **17**, 715.
Margolis, G., Odom, G. L., Woodhall, B., and Bloor, B. M. (1951). *J. Neurosurg.*, **8**, 564.
Noran, H. H. (1945). *Arch. Path. (Chicago)*, **39**, 393.
Russell, D. S. (1954). *Proc. roy. Soc. Med.*, **47**, 689.
Sterzing, P. (1908). *Zbl. allg. Path. path. Anat.*, **19**, 278.
Werner, A. (1954). *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 57.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 12

THE ACTION OF THE PHOSPHATASES OF HUMAN BRAIN ON LIPID PHOSPHATE ESTERS

BY

K. P. STRICKLAND*, R. H. S. THOMPSON, and G. R. WEBSTER

From the Department of Chemical Pathology, Guy's Hospital Medical School, London

Much work, using both histochemical and standard biochemical techniques, has been carried out on the phosphatases of peripheral nerve. It is known that this tissue contains both alkaline (Landow, Kabat, and Newman, 1942) and acid phosphatases (Wolf, Kabat, and Newman, 1943), and the changes in the levels of these enzymes in nerves undergoing Wallerian degeneration following transection have been studied by several groups of investigators (see Hollinger, Rossiter, and Upmalis, 1952).

Phosphatase activity in brain was first demonstrated by Kay (1928), and in 1934 Edlbacher, Goldschmidt, and Schläppi, using ox brain, showed that both acid and alkaline phosphatases are present in this tissue. Since that time the phosphatases have been studied in the brains of the rat, dog, sheep, rabbit, and man by a number of workers (Giri and Datta, 1936; Fleischhacker, 1938; Gordon, 1950; Reis, 1951; Naidoo and Pratt, 1951; Soulairac and Desclaux, 1951; McNabb, 1951; Pratt, 1953; Lowry, Roberts, Wu, Hixon, and Crawford, 1954). Few reports, however, are available on the distribution of the phosphatases in the grey and white matter of the brain. In dog brain McNabb (1951) has shown that both acid and alkaline phosphatases are more plentiful in grey matter than in white, but little work on their localization in human brain has so far been reported.

Furthermore, most of the studies on phosphatases have been carried out using either α- or β-glycerophosphate as substrate, or else with such unphysiological esters as phenyl phosphate, α-naphthyl phosphate, or phenolphthalein phosphate. Since, however, break-up of the fatty myelin sheath is one of the outstanding changes in the lesions of multiple sclerosis and the other demyelinating diseases, it would seem desirable to obtain more knowledge concerning the enzymic reactions associated with myelin synthesis and degradation. It was decided therefore to study the action of the phosphatases in human brain on the "lipid phosphate esters", i.e., on the various monophosphate esters that occur in the sphingomyelins, cephalins, and lecithins. In addition to α- and β-glycerophosphate we have therefore used phosphoryl choline, phosphoryl ethanolamine, phosphoryl serine, and inositol monophosphate as substrates for the phosphomonoesterases, and have measured their rates of hydrolysis by brain preparations over the *p*H range 4·5 to 10·0.

Plimmer and Burch (1937) had earlier reported that phosphoryl choline and phosphoryl ethanolamine are hydrolysed by the phosphatases of bone, kidney, and intestine, but the *p*H at which the hydrolyses were carried out was not given. In a later paper (Plimmer, 1941) it was reported that phosphoryl serine is hydrolysed by kidney and intestine phosphatase at *p*H 6·5. Roche and Bouchilloux (1947) have also stated that phosphoryl choline and phosphoryl ethanolamine are split by both acid and alkaline phosphatases; they used dog liver and intestine and beef kidney as enzyme sources, and showed that at *p*H 9 these esters are split at about the same rate as glycerophosphate. At *p*H 5·6, and using dog liver, human prostate, and beef kidney as enzyme sources, they also obtained splitting of these substrates, but at a lower rate than glycerophosphate. We have been unable to find any account of the action of phosphatases of the nervous system on either phosphoryl ethanolamine or phosphoryl serine. Baccari (1948), however, has studied the hydrolysis of phosphoryl choline by preparations of both horse intestine and brain; he found that it was rapidly hydrolysed by the alkaline phosphatase (*p*H 10 to 11) but that it was unaffected by the acid phosphatase.

In addition to reporting on the action of the phosphatases of the human brain on these lipid phosphate esters, a few observations are also described on the distribution of acid and alkaline phosphatases in certain areas of the central nervous system in man.

* Post-doctorate Overseas Fellow, National Research Council of Canada.

Since it is not possible on present evidence directly to relate the chronic nerve degeneration (Barnes and Denz, 1953 ; Cavanagh, 1954) produced by tri-*ortho*-cresyl phosphate, di*iso*propylfluorophosphonate (D.F.P.), and certain other inhibitors of the cholinesterases to an inactivation of these enzymes in the nervous system (Davison, 1953 ; Thompson, 1954), it was felt that the action of these compounds should also be studied on other esterases. Although Webb (1948) had shown that the acid and alkaline phosphatases of rabbit kidney are inhibited only by high concentrations of D.F.P. (10^{-3}M or higher), it was thought desirable to investigate the action of tri-*ortho*-cresyl phosphate and D.F.P. on the phosphatases of brain. The effect of eserine has also been examined, although there is no evidence that this compound produces chronic nerve lesions.

Experimental

Enzyme Preparations.—Human brain and spinal cord, obtained as soon as possible after necropsy, were used for the enzyme preparations.

Dialysed Homogenates.—Homogenates (1 g. brain/3 ml. H_2O) of cortical grey matter, basal ganglia, subcortical white matter, corpus callosum, and spinal cord (lumbar region) were prepared as described by Webster (1954). These homogenates were dialysed in sausage skin sacs against distilled water at 0 to 4° C. for 20 to 24 hours. The dialysed homogenates were then either used directly for phosphatase assays or were acetone dried.

Acetone-dried Preparations.—Dialysed homogenates of cortical grey and subcortical white matter were treated with 4 volumes of ice-cold acetone. The precipitate was centrifuged down and resuspended in ice-cold acetone. The precipitate was filtered off under suction and dried in air with the aid of a small volume of ether. This dried powder was dispersed in water (a weight equivalent to 250 mg. fresh wt./ml.) 15 minutes before it was to be used as a source of phosphatase.

Buffers.—All buffers were adjusted to the desired *p*H with the Cambridge *p*H meter.

0·2M *Acetate* buffer was used for the *p*H range 4·5 to 5·9.

0·2M *Glycylglycine*. This buffer was used for the *p*H range 6·5 to 8·0.

0·2M *Carbonate-bicarbonate*. This buffer was used for the *p*H range 8·0 to 10·0.

Substrates.—Stock solutions (0·15M) of each substrate were prepared. For phosphatase assays 0·2 ml. of this stock solution was added; for a final volume of 3 ml. this gives a concentration of 10^{-2} M.

The following substrates were used :—

Sodium phenyl phosphate (British Drug Houses Ltd.)

Sodium α-naphthyl phosphate (Hopkin & Williams Ltd.)

Sodium phenolphthalein diphosphate (L. Light & Co. Ltd.)

Sodium α-glycerophosphate (L. Light & Co. Ltd.)

Sodium β-glycerophosphate (British Drug Houses Ltd.)

Phosphoryl Choline.—This substrate was prepared as the calcium salt by the method of Riley (1944). Calcium was removed from a solution of this salt by the addition of sodium oxalate.

Phosphoryl Ethanolamine.—The barium salt of this compound was prepared according to the method of Outhouse (1937). Barium was removed from a solution of this salt by adding Na_2SO_4 until no further precipitation of $BaSO_4$ occurred.

Phosphoryl Serine.—The barium salt of phosphoryl serine was prepared essentially according to the method of Plimmer (1941). It was found necessary to use 100% H_3PO_4 in the preparation. This was obtained by removing the water from syrupy H_3PO_4 (s.g. 1·75) *in vacuo* at 145° C., aided by a soxhlet thimble, filled with P_2O_5 and asbestos fibre, suspended over the acid. On cooling long, plate-like crystals formed ; this crystalline H_3PO_4 was dried over P_2O_5. As for phosphoryl ethanolamine, barium was removed in the form of the insoluble sulphate.

Inositol Monophosphate.—A crude preparation of free inositol monophosphate was obtained using the method outlined in *Biochemical Preparations* (McCormick and Carter, 1952).

Inhibitors.—A fresh solution of each of the cholinesterase inhibitors was prepared of sufficient strength that 0·2 ml. of this solution in a final volume of 3 ml. gave the desired concentration. The following inhibitors were used : eserine sulphate (British Drug Houses Ltd.) ; D.F.P., kindly provided by the Ministry of Supply, Experimental Station, Porton, Wilts ; and tri-*ortho*-cresyl phosphate (T.O.C.P.) (Geigy Pharmaceutical Laboratories, Ltd.).

Incubation and Sampling.—For each experiment stoppered tubes were set up containing 1·5 ml. of buffer, 0·5 ml. of enzyme preparation, 0·1 ml. 0·03M $MgCl_2$, and 0·7 ml. water (0·9 ml. water for tubes containing no substrate). The tubes were warmed to 38° C. and then 0·2 ml. of substrate was added to each tube. One-millilitre samples were taken immediately following addition of the substrate and after 60 minutes incubation with shaking at 38° C. Each sample was added to 1·5 ml. 8·3% trichloroacetic acid in order to stop the enzyme reaction and to precipitate the protein.

The precipitate was centrifuged and a portion of the supernatant was used for the inorganic phosphate analysis.

Estimation of Inorganic Phosphate.—Inorganic phosphate (ortho) was estimated according to the method of Ernster, Zetterström, and Lindberg (1950). One millilitre of the above supernatant was added to a stoppered tube containing 5 ml. 1 : 1 isobutanol : benzene, 3·5 ml. 5% trichloroacetic acid, and 0·5 ml. 60% perchloric acid. Then 0·5 ml. of 10% ammonium molybdate was added and the tube stoppered and shaken vigorously for 30 seconds ; 2 ml. of isobutanol : benzene layer containing the phosphomolybdic acid complex were then diluted to 6 ml. with acid alcohol (32 ml. concentrated H_2SO_4/1. absolute ethanol). The blue colour was developed by

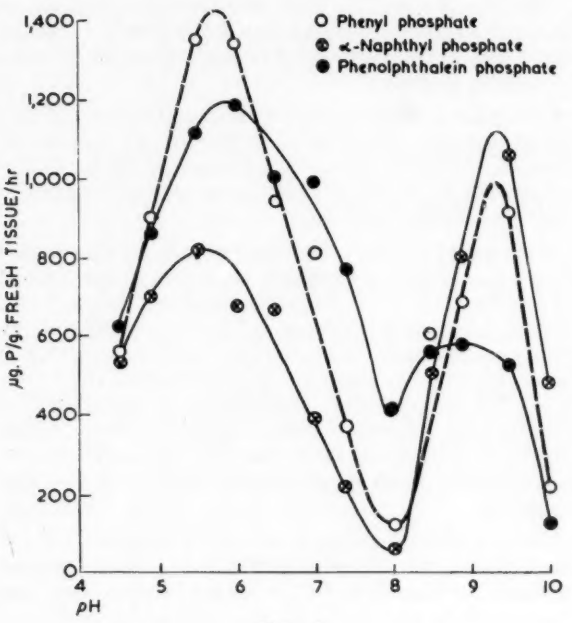


FIG. 1

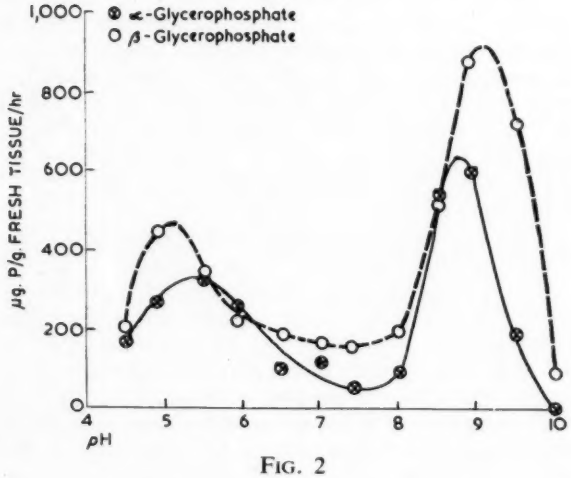


FIG. 2

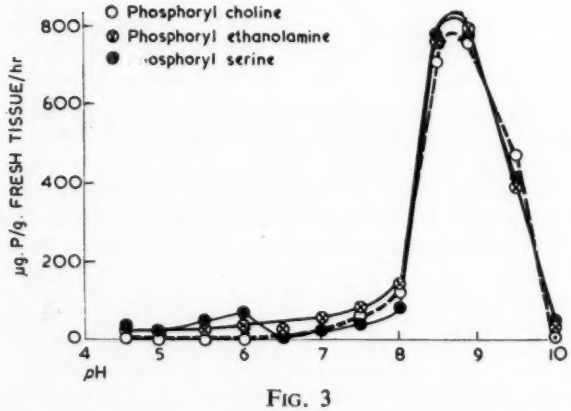


FIG. 3

adding 0·5 ml. of dilute $SnCl_2$ (stock solution of 10 g. $SnCl_2$ $2H_2O$/25 ml. concentrated HCl diluted 200 times with N H_2SO_4). This colour was read after 30 minutes on a spectrophotometer at 730 mμ.

Phosphatase Activity.—Phosphatase activities have been expressed in terms of μg. inorganic P released/g. fresh tissue/hour. In all cases, small corrections have been made for inorganic phosphate released from the tissue and for non-enzymic hydrolysis of the substrate.

Results

The rates of hydrolysis of these various substrates by acetone-dried preparations of human cerebral cortical grey matter over the *p*H range 4·5 to 10·0 are shown in Figs. 1 to 3. It will be seen (Fig. 1) that the three aromatic phosphate esters are each hydrolysed by both the acid and alkaline phosphatases. There does not appear to be any great difference in the *p*H optima for these three substrates; values ranging from 5·5 to 5·8 for the acid phosphatase and from 9·0 to 9·4 for the alkaline phosphatase being found.

The results shown in Fig. 2 indicate that under our conditions α- and β-glycerophosphate are hydrolysed by the alkaline phosphatase of human brain at approximately the same rate as that at which the aromatic esters are split. The glycerophosphates are also split by the acid phosphatase, but at a considerably lower rate than the aromatic esters. The *p*H optima for the glycerophosphates are in the neighbourhood of 5·1 to 5·5 and of 8·7 to 9·1, for the acid and alkaline phosphatases respectively.

The phosphate esters of choline, ethanolamine, and serine are also each hydrolysed rapidly by the alkaline phosphatase of brain, the rates being of the same order as those for the aromatic and glycerol esters. In contrast to these other esters, however, the choline, ethanolamine, and serine esters do not appear to be hydrolysed to any significant extent by the acid phosphatase.

The relative levels of acid and alkaline phosphatase activity in different areas of grey and white matter from the brain, and also in the spinal cord, are shown in Table I.

There does not seem to be any noticeable difference in the acid or alkaline phosphatase activity

FIG. 1.—Hydrolysis of phenyl phosphate, α-naphthyl phosphate, and phenolphthalein phosphate by acetone-dried preparations of human cerebral cortical grey matter.

FIG. 2.—Hydrolysis of sodium α- and β-glycerophosphate by acetone-dried preparations of human cerebral cortical grey matter.

FIG. 3.—Hydrolysis of phosphoryl choline, phosphoryl ethanolamine, and phosphoryl serine by acetone-dried preparations of human cerebral cortical grey matter.

of different areas of grey (cortical grey matter and basal ganglia) or white matter (subcortical white and corpus callosum). However, as can be observed from the ratios of 2·1 and 4·6 for the means of the acid : alkaline phosphatase activity of grey and white matter respectively, there is much more acid phosphatase than alkaline phosphatase in each tissue. The results for spinal cord are very similar to those for white matter, there being a much more active acid phosphatase than alkaline phosphatase. At *p*H 8·9, mean activities of 726 for grey matter and 261 for white matter were obtained using phosphoryl ethanolamine. These values are very similar to those obtained for phenyl phosphate (Table I).

TABLE I

ACTIVITY OF ACID (*p*H 5·5) AND ALKALINE (*p*H 8·9) PHOSPHATASES IN DIFFERENT AREAS OF HUMAN BRAIN AND SPINAL CORD *

	Activity		Acid : Alkaline Ratio
	Acid	Alkaline	
Grey matter			
Cortical grey	1,775	662	
" "	1,163	1,128	
Corpus striatum	1,920	574	
" "	1,613	717	
Mean	1,618	770	2·1
White matter			
Subcortical	1,267	152	
"	1,007	294	
Corpus callosum	1,201	185	
" "	1,143	368	
Mean	1,155	250	4·6
Spinal cord			
Lumbar	1,193	269	
"	1,151	257	
Mean	1,172	263	4·5

* Dialysed homogenates of each area ; phenyl phosphate as substrate. Activity expressed as μg. P/g. fresh tissue/hr.

It will further be seen that there is very much less alkaline phosphatase in the spinal cord or the white matter of the brain than in grey matter. The acid phosphatase activity of white matter, on the other hand, is only slightly less than that of the grey. These relative proportions are summarized in Table II.

In view of the presence of phosphate esters of inositol in the diphosphoinositide component of the cephalins (Folch, 1949), the action of the brain phosphatases has been studied, in a preliminary experiment, on a crude preparation of inositol monophosphate. It was found that, using an acetone-dried powder of cortical grey matter, this substrate at *p*H 8·9 was hydrolysed at a rate of 315 μg.P/g. fresh tissue/hour, but showed no significant hydrolysis at *p*H 5·5. This preliminary result, therefore, indicates that the pattern of hydrolysis of this substrate by brain phosphatases is similar to that shown by the other lipid phosphate esters.

TABLE II

RATIOS OF ACTIVITY OF PHOSPHATASES IN GREY AND WHITE MATTER OF HUMAN BRAIN (DIALYSED HOMOGENATES)

*p*H	Substrate	Activity of Grey Matter : White Matter
5·5	Phenyl phosphate	1·4
8·9	Phenyl phosphate	3·1
8·9	Phosphoryl ethanolamine	2·8

The effects of the two " demyelinating " anticholinesterases and of eserine on the acid and alkaline phosphatases of human brain, using both phenyl phosphate and phosphoryl ethanolamine as substrates, are shown in Table III. It will be seen that none of these inhibitors exerted any significant effect on either type of phosphatase.

TABLE III

EFFECT OF CHOLINESTERASE INHIBITORS ON ACID AND ALKALINE PHOSPHATASE OF ACETONE-DRIED HUMAN CEREBRAL CORTICAL GREY MATTER *

Substrate	*p*H	Phosphatase Activity in Presence of			
		No Inhibitor	Eserine (10^{-4}M)	D.F.P. (10^{-3}M)	T.O.C.P. ($1{\cdot}8 \times 10^{-4}$M)
Phenyl phosphate ..	8·9	1,350	1,402	1,252	1,382
Phosphoryl ethanolamine	8·9	647	676	661	632
Phenyl phosphate ..	5·5	1,147	1,315	1,235	1,189

* Expressed as μg.P/g. fresh tissue/hr.

Discussion

The experiments described above confirm the earlier findings of Gordon (1950) and Reis (1951) that both acid and alkaline phosphatases are present in human brain. It is clear, however, that the observed levels of each of these enzyme activities depend very markedly on the substrate used for their measurement. This is particularly so in the case of the acid phosphatase ; thus, while the glycerophosphates are split more slowly than the aromatic esters, the lipid phosphate esters are hardly attacked at all. These latter esters would, therefore, seem to be selective substrates for the alkaline phosphatase of nervous tissue. As pointed out earlier, Baccari (1948) described a similar inactivity of the acid phosphatase of horse brain towards phosphoryl choline, and we have shown that, with human brain, this applies also to the ethanolamine and serine esters, and probably also to inositol monophosphate.

It will be seen that our study of the distribution of the phosphatases in different areas of the human

brain has been limited to a very few regions. Nevertheless, we have not found any obvious difference between the two areas of grey or of white matter which we have investigated. From this preliminary survey it is apparent that our finding of a higher acid : alkaline phosphatase ratio in white matter than in grey supports the conclusion reached by Hollinger and others (1952) for cat sciatic nerve that the alkaline phosphatase is mainly neuronal in situation whereas the acid phosphatase is a sheath component, and suggests that in the central nervous system the latter enzyme is possibly associated with glial structures.

The experiments with the anti-cholinesterases indicate that levels of D.F.P. and T.O.C.P. higher than those that are likely to be found in the nervous system of animals poisoned by "demyelinating" doses of these compounds produce no inhibition of either type of phosphatase. This would seem to rule out any inactivation of brain phosphatases as a cause of the nerve degeneration produced by these anti-cholinesterases.

Summary

The effect of brain phosphatase preparations on a number of "lipid phosphate esters" has been studied.

It has been found that at *p*H 8·9 the alkaline phosphatase of human brain hydrolyses phenyl phosphate, α-naphthyl phosphate, phenolphthalein phosphate, α- and β-glycerophosphate, and the phosphate esters of choline, ethanolamine, and serine at approximately the same rate.

The acid phosphatase of human brain, on the other hand, while strongly active against the aromatic phosphate esters, hydrolyses α- and β-glycerophosphate relatively slowly and has virtually no effect on the lipid phosphate esters.

A crude preparation of inositol monophosphate has also been used as a substrate; like the other lipid phosphate esters this compound appears to be hydrolysed only by the alkaline phosphatase.

The acid : alkaline phosphatase ratio is considerably higher in white matter than in grey.

High concentrations of two "demyelinating" anti-cholinesterases (di*iso*propylfluorophosphonate and tri-*ortho*-cresyl phosphate) have been shown to cause no inhibition of either acid or alkaline phosphatase of human brain.

We wish to thank the Medical Research Council for a grant towards the expenses of this work. Our thanks are also due to Mr. D. B. Mays for technical assistance.

References

Baccari, V. (1948). *Arch. Sci. biol. (Napoli)*, **32**, 391.
Barnes, J. M., and Denz, F. A. (1953). *J. Path. Bact.*, **65**, 597.
Cavanagh, J. B. (1954). *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 163.
Davison, A. N. (1953). *Brit. J. Pharmacol.*, **8**, 212.
Edlbacher, S., Goldschmidt, E., and Schläppi, V. (1934). *Hoppe-Seyl. Z. physiol. Chem.*, **227**, 118.
Ernster, L., Zetterström, R., and Lindberg, O. (1950). *Acta chem. scand.*, **4**, 942.
Fleischhacker, H. H. (1938). *J. ment. Sci.*, **84**, 947.
Folch, J. (1949). *J. biol. Chem.*, **177**, 505.
Giri, K. V., and Datta, N. C. (1936). *Biochem. J.*, **30**, 1089.
Gordon, J. J. (1950). *Ibid.*, **46**, 96.
Hollinger, D. M., Rossiter, R. J., and Upmalis, H. (1952). *Ibid.*, **52**, 652.
Kay, H. D. (1928). *Ibid.*, **22**, 855.
Landow, H., Kabat, E. A., and Newman, W. (1942). *Arch. Neurol. Psychiat. (Chicago)*, **48**, 518.
Lowry, O. H., Roberts, N. R., Wu, M., Hixon, W. S., and Crawford, E. J. (1954). *J. biol. Chem.*, **207**, 19.
McCormick, M. H., and Carter, H. E. (1952). *Biochem. Prep.*, **2**, 65.
McNabb, A. R. (1951). *Canad. J. med. Sci.*, **29**, 208.
Naidoo, D., and Pratt, O. E. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 287.
Outhouse, E. L. (1937). *Biochem. J.*, **31**, 1459.
Plimmer, R. H. A. (1941). *Ibid.*, **35**, 461.
——, and Burch, W. J. N. (1937). *Ibid.*, **31**, 398.
Pratt, O. E. (1953). *Ibid.*, **55**, 140.
Reis, J. L. (1951). *Ibid.*, **48**, 548.
Riley, R. F. (1944). *J. Amer. chem. Soc.*, **66**, 512.
Roche, J., and Bouchilloux, S. (1947). *C.R. Soc. Biol. (Paris)*, **141**, 1068.
Soulairac, A., and Desclaux, P. (1951). *Rev. neurol. (Paris)*, **85**, 81.
Thompson, R. H. S. (1954). *Chem. and Industry*, p. 749.
Webb, E. C. (1948). *Biochem. J.*, **42**, 96.
Webster, G. R. (1954). *Ibid.*, **57**, 153.
Wolf, A., Kabat, E. A., and Newman, W. (1943). *Amer. J. Path.*, **19**, 423.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 17.

THE EFFECT OF THE DURATION OF VITAMIN-A DEFICIENCY IN FEMALE RABBITS UPON THE INCIDENCE OF HYDROCEPHALUS IN THEIR YOUNG

BY

J. W. MILLEN and D. H. M. WOOLLAM

From the Department of Anatomy, University of Cambridge

When female rabbits are subjected to an experimental vitamin-A deficiency before mating, their offspring show signs of a nervous disorder from three to six weeks after birth (Millen, Woollam, and Lamming, 1953; Lamming, Woollam, and Millen, 1954). This disorder was attributed to hydrocephalus which was present in the young animals. In a subsequent paper (Millen and others, 1954) it was reported that a congenital hydrocephalus was constantly found in young stillborn rabbits when their dam had been maintained on a vitamin-A deficient diet for periods of from 14 to 38 weeks before mating.

The initial observations on the production of hydrocephalus by a maternal vitamin-A deficiency were made on a small number of litters from an inbred strain of rabbits. Attention was drawn to the need for the substantiation of these findings (Annotation, *Brit. med. J.*, 1954). In order, therefore, to study more closely with larger numbers this relationship between maternal vitamin-A deficiency and the incidence of hydrocephalus in the young a colony of rabbits was established in 1953. In this paper the effect of maternal hypovitaminosis A upon the incidence of hydrocephalus in the young in a large number of litters is reported.

Materials and Methods

Rabbits aged 4 or 5 months were purchased from accredited dealers at monthly intervals. These does were of mixed breeds, including Dutch and Flemish rabbits and crosses. In addition some albino rabbits from the general laboratory stock were included in the experiment. It may be noted here that although litters with hydrocephalus were obtained from all the breeds used, the majority of the litters came from the smaller rabbits of the Dutch type. Five males of different varieties were employed for breeding purposes.

The rabbits were housed in standard metal cages and transferred to wooden breeding hutches one week before the expected date of parturition. Sawdust was used for both cages and hutches, and wood wool was supplied as nesting material. The animals were fed on a vitamin-A deficient pellet diet made according to the formula given by Lamming and others (1954). Water was supplied *ad libitum*. All adult animals received a weekly supplement by mouth of 50 mg. α-tocopheryl acetate and 1,500 i.u. vitamin D in 2 ml. arachis oil. The control animals received in addition 7,500 μg. vitamin A weekly in arachis oil. The males received the normal laboratory diet.

No attempt was made to breed from does on the deficient diet (deficient rabbits) until they were at least 9 months old and had been on the diet for 12 weeks or longer. Surviving rabbits from litters born to deficient dams were separated from their mothers after four weeks and fed on the same diet. Some of these young animals were subsequently killed for examination but others are still surviving in the colony. Up to the present 50 rabbits have been used in the experiment.

The presence or absence of hydrocephalus in the young rabbits was determined either by sectioning the head after freezing or by dissection after fixation. Histological examination of the material is being carried out with the object of determining the mechanism producing the hydrocephalus and it is intended to publish a report on this in a subsequent communication.

Cerebrospinal fluid pressure measurements were made on a small number of the young born to deficient dams. The pressures were measured by cisternal puncture and recorded by means of a bubble manometer (Griffith and Farris, 1942).

An outbreak of snuffles due to *Pasteurella lepisepticans* occurred in the colony in December, 1954. This disease has been responsible for the deaths of a number of the experimental animals. Apart from this outbreak the deficient animals generally remained in good condition, although xerophthalmia has appeared in some does and others have shown a tendency to develop conjunctivitis.

Results

The Incidence of Hydrocephalus in the Colony.—Thirty-two deficient animals were successfully mated. These produced, in first pregnancies, 32 litters of which one was aborted before term. In the 31 litters carried to term 142 young were born and, of these, 82 showed varying degrees of hydro-

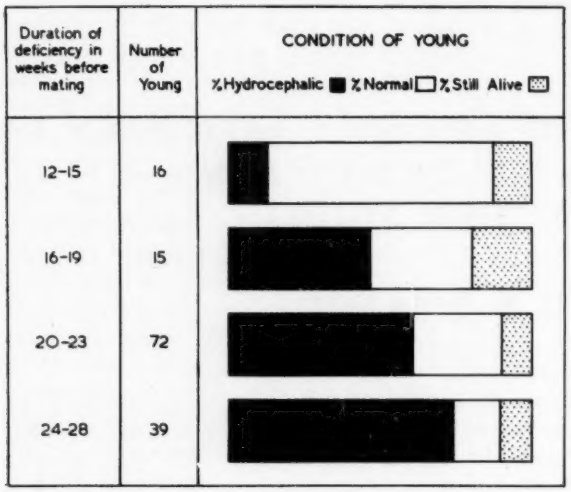


FIG. 1.—Diagram illustrating the incidence of hydrocephalus in first litters.

cephalus at post-mortem examination. In 42 young the ventricles of the brain appeared normal on section, and a further 18 are still alive. The length of time on the deficient diet before mating varied from 12 to 28 weeks. No hydrocephalus was found in 23 control young from six litters.

The results are shown in Fig. 1. The most important points which emerge are the following.

1. Dams which had been on the deficient diet for 24 to 28 weeks before mating produced many more hydrocephalic young than those which had been on the deficient diet for shorter times.

2. Of the young recorded as hydrocephalic two, born to a 24 weeks deficient doe, appeared normal at birth and were killed when 41 days old. At necropsy hydrocephalus was found in both these animals. Three litter mates of these animals are still alive.

3. Twenty-four "normal" young (including seven with increased cerebrospinal fluid pressures) were born to five does which in subsequent litters gave birth to hydrocephalic young.

4. In 27 litters the young in any one litter were either all normal or all hydrocephalic.

Measurement of the Cerebrospinal Fluid Pressure.—Cerebrospinal fluid pressure measurements made on seven young gave readings which ranged from 120 mm. to 265 mm. of water. (The average cerebrospinal fluid pressure in the rabbit is less than 100 mm. of water.) These animals were not hydrocephalic when examined later at necropsy.

Post-mortem Findings.—There was no difficulty in distinguishing the small, slit-like ventricles of the normal young (Fig. 2) from the grossly dilated ventricles seen in the hydrocephalic young (Fig. 3). In none of the hydrocephalic young examined after death was any congenital abnormality discovered other than the presence of hydrocephalus. There was no evidence of bony overgrowth in the skull. On the contrary the calvaria was very thin in the young which were stillborn or survived only a few weeks.

Discussion

The effects of a vitamin-A deficiency in the diet upon the nervous system have been frequently recorded. They include muscular incoordination and weakness, paresis, fits, and sometimes death. The mechanism by which the lesions of the nervous system are produced, however, has been a subject of controversy. Theories have ranged from a

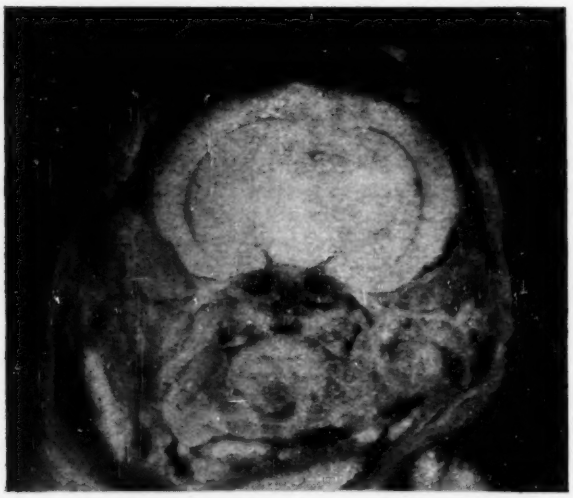


FIG. 2.—Coronal section through head of control rabbit aged 1 day. × 2·5.

FIG. 3.—Coronal section through head of hydrocephalic rabbit aged 20 days. × 2·5.

primary degeneration of the nervous system (Rigdon, 1952) to the implication of a toxic factor allied to ergot (Mellanby, 1926). Current opinion has tended to accept the view that the lesions of the nervous system are due to a disturbance of normal bone growth, itself an immediate consequence of vitamin-A deficiency. There have been two conflicting views on the nature of the disorganization. Mellanby (1938) considered that there was an overgrowth of apparently normally formed bone in certain places, whilst Wolbach and Bessey (1941) held that the fault lay in the cessation of endochondral bone formation. The present experiments would appear to show that there is a direct relationship, in rabbits, between the duration of the maternal hypovitaminosis A and the production of hydrocephalic young. There is no evidence in this study that the production of the hydrocephalus is in any way dependent upon a disturbance of bone growth. These observations make it necessary to reconsider the causes of the nervous disorders found in association with a vitamin-A deficiency in other animals.

The experiments reported in this paper suggest that the majority of the young will appear normal at birth when the degree of maternal vitamin-A deficiency is slight. It is probable, however, that many of these young have increased cerebrospinal fluid pressures. This view is supported not only by the limited number of pressure measurements made during this study but also by observations on chicks (Woollam and Millen, 1955). Some of the apparently normal young may have a minor degree of hydrocephalus at birth which produces no clinical signs and remains undiscovered until the animal either dies or is killed for examination. After more prolonged maternal deficiencies more live young can be diagnosed as hydrocephalic at birth, and, as might be expected, there are more stillborn young with hydrocephalus. Indeed, the longer the mother has been deprived of vitamin A the greater the proportion of hydrocephalic to normal live young and the greater the number of hydrocephalic stillborn.

These studies support the view that an increased cerebrospinal fluid pressure is one of the earliest signs of hypovitaminosis A (Woollam and Millen, 1955). In the absence of any evidence of pressure on the central nervous system due to a disorganization of bone growth, it must be concluded that the increase in the intraventricular pressure of the cerebrospinal fluid is responsible for the production of the hydrocephalus. Whether hydrocephalus appears or not depends largely, according to this interpretation, upon the period of growth during which the rise in pressure occurs. If the pressure rises early in gestation hydrocephalus will be present at birth. This results in stillbirth or in the production of young with enlarged and deformed heads produced by a hydrocephalus which progresses rapidly and leads to the early death of the animal. If the severity of the hypovitaminosis is less and the rise in pressure begins later in development or, perhaps, occurs more slowly, ossification of the calvaria proceeds more or less normally. Once this ossification is relatively complete it hinders or prevents further enlargement of the head. Under these circumstances an increased cerebrospinal fluid pressure is present at birth and moderate degrees of hydrocephalus may be discovered at necropsy several months later. The essential factor which determines the appearance of a gross hydrocephalus seems to be the state of ossification of the skull at the time when the rise in cerebrospinal fluid pressure is initiated.

The hypothesis that the primary factor in the pathogenesis of the condition is an over-production of cerebrospinal fluid (Millen and others, 1954) receives additional corroboration from the results of the present experiments. Moreover, only by a hypothesis such as this can the results of experiments be explained in which increased cerebrospinal fluid pressures were recorded in vitamin-A deficient animals and rapid falls in pressure occurred after the restoration of the vitamin (Helmboldt, Jungherr, Eaton, and Moore, 1953; Sorensen, Kowalczyk, and Hentges, 1954). Indeed so sensitive to vitamin-A deficiency is the cerebrospinal fluid pressure that Sorensen and others (1954) suggest it may be used as a guide to the onset of deficiency. Such a sensitivity would be extremely difficult to explain on the basis of any hypothesis which involves gross bony changes or the presence of an aqueductal stenosis as the cause of the increase in the cerebrospinal fluid pressure.

Summary

The relationship between the duration of maternal vitamin-A deficiency in rabbits and the incidence of hydrocephalus in their young has been studied.

Thirty-one litters were born at term to deficient does in first pregnancies. The length of time on the vitamin-A deficient diet for these does before mating varied from 12 to 28 weeks.

One hundred and forty-two young were born of which 82 were hydrocephalic. Eighteen are still alive and 42 showed no hydrocephalus.

The proportion of hydrocephalic young was much greater in litters from animals which had been

fed on the diet for 24 to 28 weeks before mating than from those so fed for 12 to 15 weeks.

Increased cerebrospinal fluid pressures have been recorded in seven young which were not hydrocephalic.

These results are discussed in relation to previous accounts of the effects of hypovitaminosis A in animals.

We wish to thank Professor J. D. Boyd for his advice and encouragement in the preparation of this paper; Miss I. Dean and Miss A. Smith for technical assistance; and Mr. J. F. Crane for the photographs.

This work has been supported by a grant from the Nuffield Foundation, which is gratefully acknowledged.

References

Annotation (1954). *Brit. med. J.*, **1**, 809.
Griffith, J. Q., and Farris, E. J. (1942). *The Rat in Laboratory Investigation.* Lippincott, Philadelphia.
Helmboldt, C. F., Jungherr, E. L., Eaton, H. D., and Moore, L. A. (1953). *Amer. J. vet. Res.*, **14**, 343.
Lamming, G. E., Woollam, D. H. M., and Millen, J. W. (1954). *Brit. J. Nutr.*, **8**, 363.
Mellanby, E. (1926). *J. Physiol. (Lond.)*, **61**, xxiv.
——(1938). *Ibid.*, **94**, 380.
Millen, J. W., Woollam, D. H. M., and Lamming, G. E. (1953). *Lancet*, **2**, 1234.
——, ——, ——,(1954). *Ibid.*, **2**, 679.
Rigdon, R. H. (1952). *Arch. Path. (Chicago)*, **53**, 239.
Sorensen, D. K., Kowalczyk, T., and Hentges, J. F. (1954). *Amer. J. vet. Res.*, **15**, 258.
Wolbach, S. B., and Bessey, O. A. (1941). *Arch. Path. (Chicago)*, **32**, 689.
Woollam, D. H. M., and Millen, J. W. (1955). *Nature (Lond.)*, **175**, 41.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 21.

A CLINICAL CORRELATION BETWEEN ENCEPHALOPATHY AND PAPILLOEDEMA IN ADDISON'S DISEASE

BY

ANTONY JEFFERSON *

From the Department of Neurological Surgery, Radcliffe Infirmary, Oxford

The possibility that papilloedema may occur in Addison's disease other than as a chance coincidence is not widely known. It has been possible to trace two accounts, both published since 1950, where this has been noted. This article provides an account of a third, very similar, case and also reports gross cerebral oedema in two other patients with adrenal insufficiency. Of these two patients, one had early papilloedema, and the adrenal failure was secondary to a small chromophobe adenoma of the pituitary gland. For the other patient the oedema was a feature of the post-mortem findings, but the death was so sudden and unexpected that the fundi had not been examined carefully. In discussing these patients a part of the relevant literature is surveyed and some facts about the occurrence of cerebral oedema in Addison's disease will be considered.

Case Reports

Case 1 (R.I. No. 164357/52).—The patient, a girl aged 17, was unmarried. No one in the family had had any illness similar to hers. She herself had not had tuberculosis nor was she known to have been exposed to the infection. She had never had fits.

In her past history there was nothing relevant except that her periods began when she was aged 9 and they had since been regular. The last period, which occurred two weeks before admission, was rather scanty. She had recently lost half a stone in weight. Her weight was not recorded, but it was noted that she was thin and had a poor appetite.

For a few months before admission she had found that she became short of breath when walking. There had been no ankle oedema.

Three months before admission she fell off a chair and hit her head against the wall. There was no loss of consciousness, but she did get a generalized headache which made her lie on her bed and sleep for two or three hours. She then got up for a short time but returned to bed for the rest of that day, as the back of her head was aching. The next day she felt well. Nothing further was noted until one month later when bifrontal headaches started. Initially these were mild, occurring at any time of day and lasting one or many hours. Bending down made the headaches worse. At first they occurred twice or three times a week, but as they became more severe they also became more frequent; on this account she was unable to continue her work in a dairy. She gave up reading during this period because her eyes ached when she did so. One month before admission she began to vomit, sometimes several times daily.

Three weeks before admission she fainted while standing in a bus and there were three similar "faints", all while she was standing. There were no convulsions, tongue biting, or incontinence to suggest that these were epileptic attacks.

These symptoms led to her admission to hospital, where bilateral papilloedema and bilateral extensor plantar responses were observed. Because of these findings an intracranial tumour was suspected and arrangements were made for her transfer to the neurosurgical department. Shortly before transfer she noticed some vertigo when she tried to get up from her bed; she also developed fairly persistent hiccoughs.

On admission she was found to be thin and pale. The veins in the temples were abnormally prominent. Her neck was stiff. She was not completely orientated and did not cooperate fully in the examination. She would not attempt simple arithmetical tests. She was not dysphasic but there was some dysarthria.

The fundi showed bilateral papilloedema of about 3 dioptres with a little exudate in the right fundus. The fields were full to a 5 mm. white object at 2 metres on the Bjerrum screen. Both the blind spots were enlarged. The visual acuities were normal.

She had an inconstant nystagmus on lateral gaze. There were otherwise no abnormalities in the cranial nerves. On formal bed tests the limbs showed generalized hypotonia and loss of power, together with some loss of facility in rapid coordinated movements. She objected to standing on account of the giddiness which resulted, but when persuaded to do so walked on a wide base unsteadily, deviating inconstantly to one side or the other. None of the deep tendon reflexes could be elicited. The superficial abdominal reflexes were all equally brisk. Both plantar responses were extensor. There was no disturbance of sensation.

* Nuffield Foundation Fellow.

There was no abnormal pigmentation of the skin or of the mucosae. The body hair was normal in distribution. The pulse rate was 110 per min., regular but rather feeble. The blood pressure was 95/50 mm. Hg. Examination of the chest revealed no abnormality. She would not relax the muscles sufficiently to allow satisfactory palpation of the abdomen.

Electroencephalography showed "sleep spindles" at 12 to 13 per sec. in the parasagittal leads. They were best seen in the frontal and fronto-parietal regions and occurred on a background of 5/sec. waves. A curious feature was that the E.E.G. pattern (Fig. 1), which was one consistent with light sleep, remained unchanged whether the patient's eyes were open or shut and, throughout the recording, she was able to obey simple commands.

The main clinical features of the case made it reasonable to suspect an intracranial tumour, and in order to gain more information biparietal burr-holes were made under local anaesthesia and a ventriculogram was done. The ventricles, which were small, were found in the normal position. Air was injected and the radiographs taken subsequently excluded any kind of intracranial tumour, but suggested the presence of cerebral oedema because of the sharpness of the angles of the lateral ventricles. The cause of this oedema was not identified.

While the radiographs were being taken it was discovered that the pulse could scarcely be felt and the systolic blood pressure was estimated to be 40 mm. Hg. The possibility of acute suprarenal insufficiency was considered and arrangements were made to give "eucortone" and intravenous fluids. However, before these were actually begun the blood pressure rose to 100/70 mm. Hg. (Chloride, sodium, and potassium studies were done immediately after the collapse; in retrospect these suggested an impending Addisonian crisis but their significance was not grasped at the time, the picture having been confused by the clinical features of the case.) Eucortone, 40 ml., and 1,800 ml. of fluid were given intravenously. Her blood pressure did not rise any further, and because her improvement antedated the intravenous therapy it was difficult to assess how much further livening in her state could be attributed to the "eucortone" and the fluid intake. The intravenous medication was stopped both for lack of definite evidence that it was beneficial and out of fear of making the cerebral oedema worse. The patient continued restless and disorientated, her blood pressure remaining in the region of 90/50 until she quietly and suddenly died some 36 hours after the ventriculogram.

At necropsy the lungs were normal. The heart was small, weighing 170 g. All the abdominal organs were normal with the exception of the suprarenal glands which

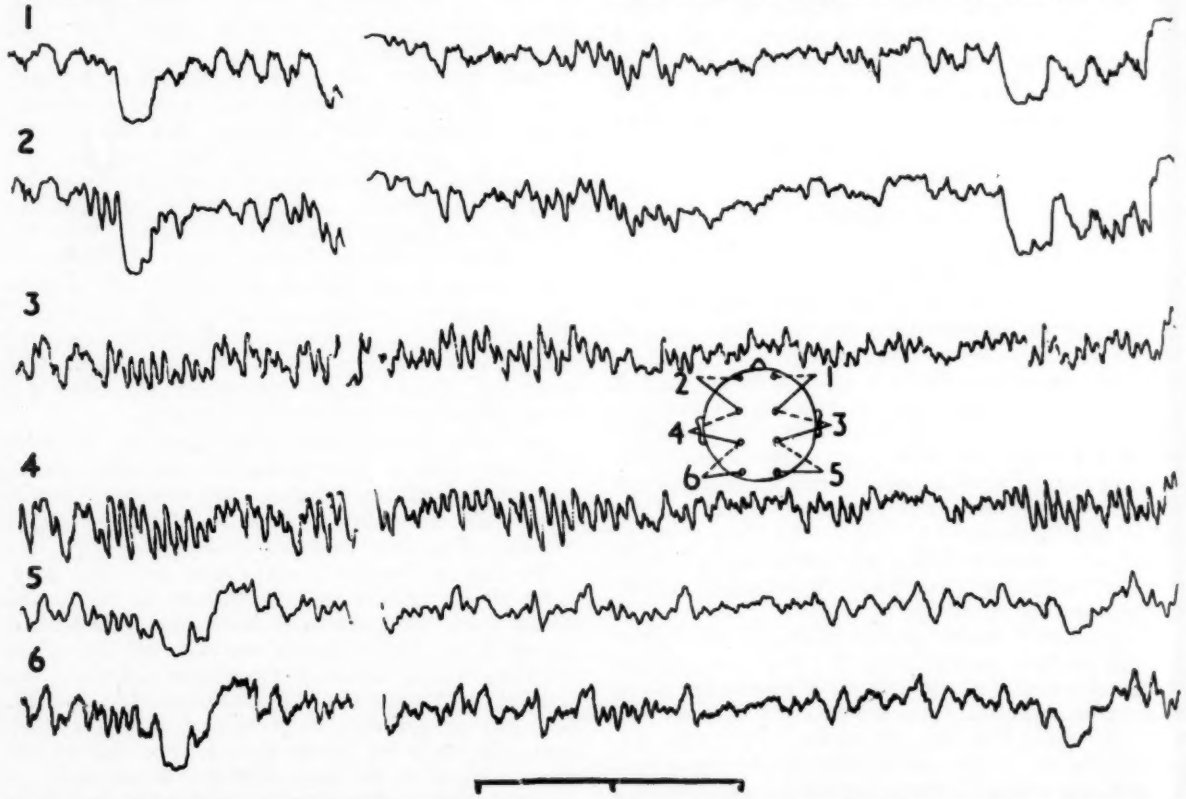


FIG. 1.—Six-channel electroencephalogram recorded from Case 1. Diagram indicates position of electrodes. Big slow waves at the left- and right-hand ends of this record are caused by eyeblinks confirming that the patient was "awake" during the recording. Record, however, shows fast beta activity closely resembling sleep spindles. (Time marker = 1 sec. intervals.)

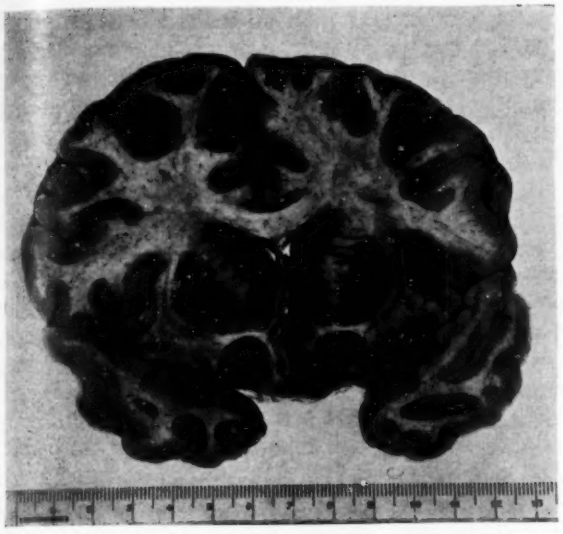


FIG. 2.—Coronal section through the frontal region to show the pathologically small lateral ventricles in Case 1.

weighed 3 g. each (normal 3·5 to 6·0 g.). On section they appeared thin and grey and there was no macroscopical evidence of yellow cortical tissue. Although a search was made for aberrant cortical tissue, none was found. Microscopical sections showed that though the adrenal medulla was intact, the cortex was entirely absent in many places and only a few islands of cortical cells were left. The blood vessels in what remained of the adrenal cortex were unduly prominent and there was some lymphocytic infiltration in the gland.

The thymus was larger than is usual at this age: it weighed 22 g. and had two main lobes and a smaller central lobe. Among the lymph glands the cervical glands alone were enlarged, a possible result of the fact that the tonsils were enlarged and infected. The thyroid weighed 12 g. (normal 30 to 40 g.) and lymphoid follicles were scattered among the colloid vesicles. The parathyroids were not found. The pituitary appeared normal but no detailed cell counts were done.

The brain weighed 1,430 g. (normal 1,230 g.). The meninges were normal with no suspicion of exudate. Examination of the base of the brain showed slight grooving of the right uncus and slight herniation of the right tonsil. These changes were not definite enough to indicate that herniation of an oedematous brain either at the tentorial hiatus or at the foramen magnum had contributed to her death. When the brain was sectioned it was found to be very full and the ventricles were small (Fig. 2). It was somewhat congested. Microscopical examination confirmed the presence of oedema and, disposed around occasional vessels, there were collections of "round cells".

Case 2 (R.I. No. 9798/43).—This 23-year-old single man had, from the age of 10 years, been subject to episodes of loss of appetite, refusal to drink, and mild headache, each lasting two to three days at a time. As he grew older he was observed to be unusual in that he never needed to shave, the body remained almost hairless, and the genitalia were underdeveloped.

Eighteen months before admission he was first aware of visual failure. In view of the features of suprarenal and other endocrine deficiencies, operation was deferred for some four months after the diagnosis of chromophobe pituitary adenoma had been made.

He was rather obese, and had a blood pressure of 90/60 mm. Hg, falling to 50 mm. Hg (systolic) on standing. As mentioned above, the secondary sex characteristics were not normally developed. Both optic discs were pale, and in addition showed early papilloedema. Vision in the left eye was reduced to hand movements, and in the right eye, although normal acuities were preserved, there was a dense temporal field defect. There were no other significant neurological abnormalities. The skull showed increased "digital impressions" suggesting raised intracranial pressure.

At operation (June 23, 1943, Mr. J. B. Pennybacker) the brain was so tight as to make considerable technical difficulties. During the course of the operation it was demonstrated that the "tightness" was not due to a big tumour nor to obstructed lateral ventricles; in fact, the lateral ventricles were unusually small and undisplaced. At the time, the significance of this observation was not known, but in the light of the cases recorded here it may be surmised that this patient also had cerebral oedema associated with the clinical evidence of suprarenal insufficiency. However, since the patient survived the operation, proof of this contention is not possible.

The finding of papilloedema in association with Addison's disease as occurred in Case 1 might be regarded as a mere coincidence were it not that two further very similar cases have been reported in the literature since 1950.

Case of Boudin, Funck-Brentano, and Gayno (1950).—This concerned a girl of 23 whose periods had begun at the age of 10. She had her first pregnancy aged 14 and her second aged 21, after which she developed persistent fatigue. Three months before admission she developed a severe and continuous occipital headache. Her gait was unsteady. She was referred to hospital because these symptoms had led to the discovery that she had considerable bilateral papilloedema.

In view of the story of headache, vomiting, and ataxia associated with papilloedema, she was admitted with a provisional diagnosis of cerebellar tumour. The general examination disclosed a slight generalized pigmentation of the skin.

A ventriculogram was proposed but the patient became acutely ill during the procedure. Her blood pressure fell to a very low level. Tapping the ventricles had provided information which made a cerebellar tumour unlikely, and the examination was discontinued without outlining the ventricular system by the injection of air.

Because the patient was considerably anaemic (R.B.C. 2,500,000) she was treated with vitamin B_{12} in the first instance and her general condition improved; the papilloedema also regressed. However, in spite of the

continued administration of vitamin B_{12} the patient relapsed and was started on a régime of 10 mg. D.O.C.A. and 6 g. salt daily. About five or six weeks after the beginning of all treatment the fundi were slightly blurred and the veins dilated.

This patient unfortunately died some two to three weeks later in an acute allergic reaction whose precipitating cause was not identified.

At necropsy it was impossible to find the suprarenal glands and presumably they were either aplastic or atrophied. The pituitary gland appeared normal. Necropsy confirmed that there was no intracranial tumour and showed diffuse and considerable cerebral oedema. The significance of the latter finding is difficult to gauge in the presence of bilateral acute pulmonary oedema secondary to the anaphylactic reaction.

Case of Walsh (1952).—This concerned a girl of 20 who had been anaemic for five years following severe pyelonephritis. Five months before admission to hospital she began to complain of excessive fatigue and of headache associated with vomiting. The diagnosis of Addison's disease had been made three months before admission.

At the time of her admission to hospital she was extremely feeble and had a severe headache and was vomiting. She had no complaints referable to the eyes. On the right side there were 3 dioptres of papilloedema and on the left side 4 dioptres. The blind spots were correspondingly enlarged. There were superficial fresh-looking exudates associated with the papilloedema but no haemorrhages. The retinal veins were full. Her blood pressure was 90/60 mm. Hg.

In view of the headache, vomiting, and papilloedema it was initially intended to investigate the nervous system. However, a lumbar puncture was not thought advisable in the presence of such a degree of papilloedema, and the dangers of ventriculography in the presence of suprarenal insufficiency were recognized. It was suggested that the papilloedema might have resulted from thrombosis of the intracranial dural sinuses and the decision was taken to treat the patient with D.O.C.A. and with cortisone and to await results.

The results were impressive. After four weeks of treatment the headache had disappeared and the blood pressure was near normal. The papilloedema had subsided to 2 dioptres. Three months later there was only slight blurring of the discs and the exudate had gone. At the time of publication the patient was still alive and well.

" Encéphalopathie Addisonienne "

Thomas Addison's paper " On the Constitutional and Local Effects of Disease of the Supra-renal Capsules " (1855) described 11 patients who came to necropsy. In seven of these the brain was not examined ; in one the brain was normal, two showed atrophy, and in one (Case 4) the grey matter of the cerebrum was of a rather deep colour. The brain was in other respects normal. Presumably there was no oedema noted. Ettlinger and Nageotte (1896) reported that in animals cerebral oedema was a frequent finding after ablation of the suprarenals. They considered the possibility that this might not be specific, but might be " agonal " in origin.

Klippel (1899) coined the term " encéphalopathie addisonienne " in relation to a 57-year-old man with typical clinical features of Addison's disease who had two fits, the first 10 days before his admission and the second immediately before admission. He was under observation for some time and was observed to have episodes of abnormal behaviour, some of which apparently culminated in convulsions. Eventually the patient died in coma. Necropsy revealed both fibrous tuberculosis of the lungs and caseating tuberculous lesions which had destroyed the suprarenal glands. The meninges were normal. The brain was oedematous. Microscopic study showed the arterioles in the grey matter to be hyperaemic, and from these vessels there had been diapedesis of numerous round cells.

The cerebral oedema observed in this case may well have been similar to that recorded in Case 1.

Frette (1913), Lebrun (1937), and Gosset (1941) all published theses which concerned themselves with the encephalopathy of Addison's disease. Frette recounts eight case histories where adrenal insufficiency and changes referable to the nervous system coexisted. Some of the cases were collected from the literature and in none of them is there any reference to the appearance of the fundi. In none of the cases, save Klippel's (mentioned above), was there any cerebral oedema, though cerebral congestion was sometimes reported. Lebrun's (1937) patient was a woman, aged 28, admitted in semi-coma with meningism. She died the same evening. At necropsy tuberculous destruction of the adrenals was revealed. The brain showed diffuse oedema with slight opacity of the meninges. The arterioles in the grey matter were hyperaemic and diapedesis of cells had occurred into the surrounding tissues. There was some oedema of the cortical cells. Gosset's (1941) two original cases of Addison's disease with cerebral symptoms are of some interest but the findings are not clear cut. In the case of a man aged 25 there was meningism and confusion, but the brain though congested showed only " slight oedema". The other patient (a woman aged 27) was admitted after stupor had lasted eight hours and died 12 hours later. This patient had a series of opisthotonic attacks accompanied by extensor spasm. It may be supposed that cerebral oedema had led to herniation of the brain, which in turn was responsible

for these symptoms, but this is only supposition since permission for a necropsy was not obtained.

Paulian, Bistriceanu, and Cardas (1941) report a further instance of a man with Addison's disease who presented terminally with neurological disturbances and was found at necropsy to have cerebral oedema, but the picture was complicated by the presence of a diffuse sclerosis of the brain. Wells (1930) described a series of cases of Addison's disease. His Case 4 concerned a woman (aged 51) who died after three weeks of a subacute illness which was marked by neurological symptoms and signs. At necropsy, apart from atrophy of the suprarenal glands and lymphoid infiltration of the thyroid, the brain tissue was oedematous; no other significant cerebral changes were found. Duffin (1943) reported another example of suprarenal atrophy accompanied by cerebral oedema. This patient (Duffin's Case 8) was a boy (16 years old) who had had several attacks of coma or semi-coma which had brought him to hospital. He was finally admitted moribund after a short period of unconsciousness. At necropsy there was loss of suprarenal cortex, and the pituitary showed a diffuse fibrosis of the anterior lobe and a reduced volume of secretory cells. There was a normal ratio between the chromophobe cells and the acidophils but the basophils were abnormally scarce. The brain was described as oedematous and increased in weight.

Guttman's review (1930) of the pathological features of Addison's disease made no comment on changes in the fundi or in the central nervous system.

In the records of the Radcliffe Infirmary, Oxford, it has been possible to trace 19 patients in the past 10 years in whom a clinical or a post-mortem diagnosis of Addison's disease has been made. In Case 1 alone was clinical evidence of raised intracranial pressure recorded. Among the cases that came to necropsy cerebral oedema was noted on four further occasions. One patient (a woman, aged 44, R.I. No. 116468/51) had suffered from lassitude and headaches and after a sudden and unexpected death the brain was found to be soft and oedematous. In another patient (a woman aged 38, R.I. No. 201987/54) considerable cerebral oedema with tentorial herniation was found (brain weighed 1,258 g.) after death, but she had been artificially respired for nearly 24 hours after spontaneous respiration ceased and it is possible that the oedema developed during this phase. In the third patient (a boy aged 10, R.I. No. 200315) Addison's disease and a mild degree of diabetes mellitus were associated. Shortly before death the diabetes became less severe. Death occurred within an hour after a sudden and unexpected collapse. On the day of death there was biochemical evidence of suprarenal failure, and necropsy confirmed considerable destruction of the suprarenal cortices. The pituitary gland appeared normal. The brain weighed 1,480 g. (normal, 1,300 g.), but it is possible that some or all of this oedema developed terminally because, following the collapse, the patient received 1,000 ml. of plasma intravenously in an effort to restore the failing circulation. The fourth patient is described below.

Case 3 (R.I. No. 147736/54).—This patient, a boy aged 3, had been in hospital seven months earlier because of convulsions. He was admitted *in extremis* and died within three hours. Addison's disease was suspected terminally but there was no time to begin effective treatment. He had been vomiting and had had episodes when, without losing consciousness, he " seemed in a trance". The day before death he became drowsy, listless, pale, and cyanosed. It is not known whether he complained of headaches nor is there a record of the appearance of the fundi. The post-mortem findings confirmed the diagnosis of suprarenal failure. The pituitary gland appeared normal. The brain was full and oedematous and weighed 1,319 g. (normal about 1,100 g.). On coronal section the ventricles were seen to be very small. Microscopical sections of the brain showed that, as in Case 1, a few blood vessels showed round cell " cuffing".

Discussion

In Case 1, and in the cases reported by Boudin, Funck-Brentano, and Gayno, and by Walsh, there can be no doubt that papilloedema and Addison's disease coexisted, and all of them had similar cerebral symptoms. In Cases 1 and 3, which came to necropsy in this hospital, and in Case 2, which was observed at operation, there were no complicating factors which might have contributed to the cerebral oedema. Thus, it seems reasonable to regard the suprarenal insufficiency as responsible for the cerebral oedema. How frequently this may happen is unknown.

Cases 1 and 3 occurred in the same hospital within the space of exactly two years and, with the exception of Case 2, all four cases mentioned in the preceding paragraph were observed within a period of less than five years. These facts, taken together with the suggestive but less clear-cut evidence of the other cases mentioned, provide a firm basis for the belief that suprarenal insufficiency is responsible for the observed oedema.

If it be conceded that suprarenal insufficiency may lead to oedema of the brain or optic nerve head, it becomes of interest to know how this is

brought about. There is as yet no definite information upon this point. There are only speculations.

Boudin and others (1950) were of the opinion that the observed oedema might result from the disturbed water metabolism known to occur in Addison's disease (e.g., Levy, Power, and Kepler, 1946). Walsh (1952), on the other hand, considered thrombosis of the intracranial dural sinuses the most likely relevant factor. In Case 1 reported here the latter possibility was considered, and a very careful examination of the dural sinuses was made at the necropsy without revealing any pathological changes in them. Moreover, sections of the brain revealed no microscopical evidence of thromboses. In Walsh's case the fundi were undoubtedly beginning to subside after only four weeks of treatment by cortisone and D.O.C.A. Most cases of "pseudotumour", in which thromboses of the dural sinuses are with good reason suspected to have occurred, have run a more prolonged course than this. Thomas (1933) and McCullagh (1941) both quote examples of patients with oedema developing at the menstrual period, who also suffered from papilloedema. In both instances the oedema of body and of nerve head subsided coincident with hormone treatment, and metabolic abnormalities may have been responsible for the oedema. It may thus be tentatively suggested that the cerebral oedema described here results from a metabolic disorder, but the matter is most certainly non-proven as yet.

Boudin and others (1950, p. 1742), in reporting their case, make the statement that this experience entitles them to speak of a definite form of pseudotumour in Addison's disease associated with cerebral oedema. The diagnosis of "pseudotumour" or "benign papilloedema" is usually attached to a patient who presents with papilloedema and indefinite neurological abnormalities which are not progressive. Moreover, general well-being of the patient is one of the features which help to make this diagnosis acceptable. However, if the papilloedema results from Addison's disease, a sense of well-being is not likely to be present.

The experience of Case 1 reported here serves as a reminder that abnormal pigmentation of the skin or mucous membrane is not a universal phenomenon in Addison's disease. The diagnosis of suprarenal failure may not be one that would readily be considered, and the present writer would suggest that Addison's disease should be included as a possible diagnosis in all cases of "benign papilloedema". This means that the serum sodium and potassium should be estimated, together with the plasma chlorides. If a suprarenal crisis is not impending, these values may be within normal limits, and it then becomes necessary to determine the "Kepler Index" (Robinson, Power, and Kepler, 1941). Whatever the value of the index if the water metabolism is abnormal and a volume of urine smaller than normal is excreted in the four hours after ingestion, then the test should be repeated with 50 mg. of cortisone given by mouth four hours before the loading dose of water (*cf.* Oleesky and Stanbury, 1951). If cortisone restores to normal the amount of water excreted in the first four hours, then a trial period of regular cortisone therapy should be begun. Cortisone 12·5 mg. eight-hourly, should suffice, with added desoxycorticosterone acetate (D.O.C.A.) if the biochemistry is, or remains, abnormal. During the trial period of treatment careful neurological supervision and regular measurement of the visual acuity and of the size of the blind spots is necessary. Walsh's (1952) experience indicates that by the end of a month there will be clear indication of the effectiveness of such treatment.

If the possibility be borne in mind that suprarenal insufficiency may lead to oedema of the optic nerve head or of the brain it should be possible to collect further information about the occurrence of this phenomenon and about its mechanism.

Summary

In a recent period of two years two cases have come to necropsy in this hospital in which cerebral oedema and suprarenal insufficiency have been associated.

One of the above cases presented with papilloedema and slight neurological abnormalities. Two very similar cases are described in the literature. All these three cases were observed within three years.

A search of the Radcliffe Infirmary records and of the literature has disclosed some further cases in which definite cerebral oedema was found at necropsy accompanying destruction or atrophy of the suprarenal cortex. In some of these examples the possibility of complicating factors cannot be excluded.

It is suggested that suprarenal failure is causally related to the oedema of the brain or a nerve head. The possible mechanisms are briefly discussed.

I would agree with Boudin, Funck-Brentano and Gayno (1950) that this syndrome might be found more commonly once the possibility of its occurrence is suspected.

I am grateful to Mr. Joe Pennybacker for encouragement and advice during the preparation of this paper. I am also obliged to Dr. F. G. Hobson, to Dr. V. Small

peice, and to Dr. H. F. Ellis for permission to publish details of patients who were under their care.

I am grateful to Dr. S. Strich for her opinion on the microscopical appearance of the pathological specimens.

REFERENCES

Addison, T. (1855). *On the Constitutional and Local Effects of Disease of the Supra-renal Capsules*. Highley, London.

Boudin, G., Funck-Brentano, J.-L., and Gayno, M. (1950). *Bull. Soc. méd. Hôp., Paris*, **66**, 1736.

Duffin, J. D. (1943). *Arch. Path.* (*Chicago*), **35**, 649.

Ettlinger, C., and Nage[illegible]te, J. (1896). *C.R. Soc. Biol.* (*Paris*), 10 ser., 3, 966.

Frette, L. (1913). *Contribution à l'étude de l'Insuffisance Surrénale aiguë à forme encéphalopathique*. Thèse, Paris.

Gosset, A. E. M. (1941). *L'Encéphalopathie addisonienne*. Thèse, Bordeaux.

Guttman, P. H. (1930). *Arch. Path.* (*Chicago*), **10**, 742, 895.

Klippel, M. (1899). *Rev. neurol.* (*Paris*), **7**, 898.

Lebrun, R. (1937). *Contribution à l'étude de l'encéphalopathie addisonienne*. Thèse, Paris.

Levy, M. S., Power, M. H., and Kepler, E. J. (1946). *J. clin. Endocr.*, **6**, 607.

McCullagh, E. P. (1941). *Cleveland clin. Quart.*, **8**, 202.

Oleesky, S., and Stanbury, S. W. (1951). *Lancet*, **2**, 664.

Paulian, D., Bistriceanu, J., and Cardas, M. (1941). *Bull. Soc. méd. Hôp. Paris*, **57**, 34.

Robinson, F. J., Power, M. H., and Kepler, E. J. (1941). *Proc. Mayo Clin.*, **16**, 577.

Thomas, W. A. (1933). *J. Amer. med. Ass.*, **101**, 1126.

Walsh, F. B. (1952). *Arch. Ophthal.* (*Chicago*), **47**, 86.

Wells, H. G. (1930). *Arch. Path.* (*Chicago*), **10**, 499.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 28.

BENIGN INTRACRANIAL HYPERTENSION

BY

PETER BRADSHAW

From the Department of Neurological Surgery, the Radcliffe Infirmary, Oxford

A common problem in neurological practice is that of the patient with papilloedema who, on investigation, is found to have neither a brain tumour nor other space-occupying lesion, nor indeed any very well defined cause to explain it. These cases have hitherto been described under the several titles of " benign serous meningitis ", " otitic hydrocephalus ", and, in the American and Continental literature, as " pseudotumour ".

This paper is concerned with an analysis of 42 such cases, admitted to the Nuffield Department of Surgery at the Radcliffe Infirmary, between the years 1938 and 1954 inclusive. Its purpose is to present information about the diagnosis, prognosis, and treatment which may be of value.

The term " otitic hydrocephalus " was introduced by Symonds (1931, 1932) owing to the frequent concurrence of aural suppuration. In such cases the distinction from brain abscess is of the greatest importance, and he stressed certain features which favoured a diagnosis of otitic hydrocephalus: namely, the absence of constitutional symptoms and focal signs, and the presence of a normal cerebrospinal fluid (C.S.F.) under increased pressure. He considered that the condition was related to accretion of blood clot in the lateral sinus and, more recently (1952), has discussed the pathogenesis with regard to possible increased C.S.F. formation, cerebral oedema, and defective absorption of C.S.F.

Both an increase of C.S.F. formation and cerebral oedema might ensue if there were obstruction to the intracranial venous outflow. Indeed, Sugarbaker and Wiley (1951) have shown that, following bilateral jugular ligation in man, a transient intracranial hypertension develops. But, as Symonds pointed out, unless the opposite lateral sinus is rudimentary, a thrombosis upon one side would have to extend to the torcula in order to effect complete obstruction. In such cases compression of the jugular veins would fail to provoke a rise of the spinal C.S.F. pressure, and in most patients with otitic hydrocephalus the manometric observations are normal. However, Nielsen and Courville (1934) have shown that this mechanism may occasionally be incriminated. In their study of 42 patients who died with a lateral sinus thrombosis they found an extension of the thrombus into the posterior portion of the sagittal sinus in six. A similar observation was made by Bailey and Hass (1937) in a patient who died with otitic hydrocephalus. In addition, Symonds (1952) described a young woman with otitic hydrocephalus who expired after a lumbar puncture. At necropsy she was found to have a thrombosis of a lateral sinus which extended upwards into the posterior end of the superior longitudinal sinus and downwards into the jugular vein as far as its junction with the common facial vein.

The presence of cerebral oedema has at times been suggested by ventriculography. Davidoff and Dyke (1936) attempted a ventriculogram on each of 12 patients with " benign serous meningitis "; in six the ventricles were difficult to locate with the brain needle and failed to fill with air, in the remainder the ventricles were smaller than normal. Dott (quoted by Symonds, 1952) has also remarked on the small size of the cerebral ventricles in the acute stage of the condition.

The experimental observations of Weed (1914) have shown that when the arachnoid villi in animals are blocked with lamp black hydrocephalus ensues. This led Symonds (1932) to suggest that a mural thrombosis of the sagittal sinus, arising from the lateral sinus, might interfere with C.S.F. absorption by the arachnoid villi. This mechanism would explain the syndrome of otitic hydrocephalus, and some support for this theory is gained by the results of sinography. By this means, Frenckner (1937) and Ellis (1937) were able to demonstrate occlusion of the sagittal sinus during life.

McKenzie (1948) and others have criticized the label " otitic " since infections of the second branchial cleft are not exclusive in the production of the syndrome. McAlpine (1937) reported the association with non-suppurative inflammations of the nasopharynx, Symonds (1937) with puerperal thrombosis of the leg veins, peritonsillar abscess,

thrombophlebitis migrans, and (1940) with frontal sinusitis. Garcin and Pestel (1949), in a detailed review of the literature, have incriminated trauma, cachexia, and anaemia.

Symonds (1937) has reminded us that the pterygoid venous plexus, which drains the upper respiratory tract, including the tonsillar bed, is a tributary of the jugular vein. Garcin and Pestel (1949) have shown that this plexus also communicates with the cavernous sinus. Symonds suggested that a thrombosis of veins in the locality of the tonsils might extend to involve first the internal jugular vein and from thence into the intracranial venous sinuses and thereby explain the development of papilloedema in patients with tonsillitis. A somewhat similar accretion of clot may follow thrombosis of the jugular vein related either to trauma or to cervical lymphadenitis (Garcin and Pestel, 1949). Pennybacker (1943) described a patient with a thymic tumour who developed papilloedema. At necropsy the tumour was found to have compressed the left innominate vein and, from this site, a thrombosis extended up the jugular vein into the major intracranial venous sinuses.

The syndrome of cortical thrombophlebitis was first described by Martin and Sheehan (1941) in women during the puerperium and patients with gastro-intestinal infections. Unlike otitic hydrocephalus, the condition is characterized by constitutional symptoms, focal signs referable to one or both cerebral hemispheres, and fits. In addition, Martin and Sheehan found in many that the C.S.F. was bloodstained or contained an excess of cells or protein. They considered that the condition arose as the result of embolic spread, via the spinal venous plexus, from a local thrombosis of pelvic veins. In support of this theory they quoted the observations of Baston who injected radio-opaque material into the pelvic veins. After compression of the abdomen he was able to demonstrate the contrast medium within the cranium.

The prognosis is less favourable than in otitic hydrocephalus and a number of cases came to necropsy. Martin and Sheehan reported the presence of thrombosis of cortical veins, cerebral softening and oedema, and the finding of punctate haemorrhages within the brain and meninges. An interesting but unusual cause of death, noted by Garcin and Pestel (1949), was thrombosis of the great vein of Galen with resulting softening and infarction of the basal ganglia. These authors were loth to accept the theory of venous embolism. They have remarked that though a few of the puerperal cases gave a history of complications, such as "white leg" or haemorrhages, the majority had normal pregnancies. Kendall (1948) has suggested that the increased blood fibrinogen or number of circulating platelets, known to occur in late pregnancy, or the presence of new and "sticky" red cells recently withdrawn from the bone marrow in response to haemorrhage, were factors which accounted for the puerperal incidence.

The close relationship between otitic hydrocephalus and cortical thrombophlebitis is emphasized by Symonds (1937) and Garcin and Pestel (1949) who have described the concurrence of both conditions. Indeed this is not remarkable, since in the first there is a high incidence of thrombosis of venous sinuses whilst in the second the veins are involved. Barnett and Hyland (1953) have shown that factors which predispose to extracranial venous thrombosis are also associated with thrombosis of veins within the skull. These include cardiac disease, cachexia, post-operative and post-traumatic states, hyperpyrexia, haemorrhage, and certain rare blood dyscrasias.

In the treatment of otitic hydrocephalus, with or without involvement of cortical veins, most authorities, including Symonds, Garland and Seed (1933), and McKenzie (1948), have recommended repeated spinal puncture to avert the development of consecutive optic atrophy. Others, including Davidoff and Dyke (1936), have employed yet more energetic methods and supplement this régime with dehydration therapy and operative decompression.

Clinical Material and Presentation of Cases

It was found that the 42 patients fell into five clinical groups by reason of an associated pathology as follows: (1) Infections of the second branchial cleft and respiratory tract (26 cases, 61%); (2) extracranial venous thrombosis (four cases); (3) obesity (six cases); (4) post-traumatic (two cases); (5) undetermined (four cases).

The age and sex distribution of the several groups is shown in Table I.

TABLE I
AGE AND SEX DISTRIBUTION

Age Group (years)	Group 1		Group 2		Group 3		Group 4		Group 5	
	M	F	M	F	M	F	M	F	M	F
2½–10	6	7	0	0	0	0	1	0	0	0
11–20	4	3	0	0	1	0	0	0	1	0
21–30	0	4	0	1	0	2	0	0	0	1
31–40	0	2	0	1	0	2	1	0	1	1
41–52	0	0	1	1	0	1	0	0	0	0
Totals	10	16	1	3	1	5	2	0	2	2

Infections of Second Branchial Cleft and Respiratory Tract.—The majority of the patients (61%) had conditions clearly associated with infections of

the second branchial cleft or respiratory tract. Twenty-one patients (50%) had aural suppuration and these were classical examples of otitic hydrocephalus ; they provided much of the information which was applied later to the other groups. In brief, it is generally the story of a child who has had a recent aural infection, develops a squint due to paralysis of one or both external rectus muscles, and complains of headache. This leads to examination of the optic fundi and to the discovery of papilloedema. In many cases there is no headache.

Case 1 (*No.* 79323/47).—Ten weeks before admission to this hospital this child, a boy aged 5, had a left Schwartz mastoidectomy for an acute mastoiditis. After a fortnight the wound was healed and he returned home. At this time his parents noticed that he had a squint, though he did not complain of headache or any other symptoms. He was admitted to the Radcliffe Infirmary because his doctor had detected papilloedema and rightly suspected that he might have a brain abscess.

On examination he was an alert and intelligent boy with a head circumference of 21 in. (normal 19·8 in.), which gave a cracked-pot note to percussion. There was bilateral papilloedema of 2 dioptres, and the visual acuities were preserved. The left external rectus muscle was paralysed, but there were no other abnormal physical signs ; in particular, there was no hemianopia.

Radiographs of the skull showed increased convolutional markings and moderate suture diastasis. The lumbar C.S.F. pressure was 220 mm. of water, the spinal manometric observations were normal, and the fluid contained 1 lymphocyte per c. mm. and 15 mg. of protein per 100 ml. A ventriculogram showed very slight dilatation of otherwise normal ventricles.

All the evidence pointed to this being otitic hydrocephalus and he was discharged from hospital without treatment after eight days. He remained in good health ; the squint cleared up in two months and the appearances of the optic fundi were normal within eight months.

This case illustrates the remarkably symptomless course of the malady which was detected only because the child developed a squint.

Table II shows the nature of the infection giving rise to intracranial hypertension. Of the nine patients who had a mastoidectomy, the lateral sinus was reported to be thrombosed in two and normal in seven. The time interval between operation and the detection of papilloedema was from one to 49 days, with an average of 19 days. Three of the patients who had otitis media had sustained a mild head injury which was followed by an exacerbation of the pre-existing aural disease. All the evidence suggested that the raised intracranial pressure which developed arose in connexion with otitis rather than with the injury, though the two cases in Group 4 seemed to be purely traumatic in origin.

TABLE II
PREDISPOSING INFECTION

Nature of Infection	No. of Cases
Post-mastoidectomy	9
Acute otitis media	11
Chronic otitis media	1
Acute follicular tonsillitis	2
Frontal sinusitis	2
Pulmonary abscess	1

The following remarkable case shows that very occasionally the pathological process giving rise to otitic hydrocephalus is not confined to intracranial structures.

Case 2 (*No.* 118074/50).—Since the age of 5 this girl, now aged 15, had suffered from a recurrent left-sided otorrhoea and, at the age of 8, the tonsils and adenoids were removed. Five weeks before admission to this hospital she developed an acute left mastoiditis for which an endaural mastoidectomy was done. At operation the left lateral sinus was reported to have been normal. Post-operative recovery was uneventful until the fourth day when she vomited and was found to have a stiff neck, papilloedema, and a pyrexia of 101° F. She was transferred to the Radcliffe Infirmary on February 22, 1950.

On examination she was a thin, pale, and ill-looking girl with a fever of 100° F. There was marked neck stiffness and Kernig's sign was positive. The blind spots measured some 30 in. in diameter at 2 m. and the visual acuity was J2, 6/18 on the right and J2, 6/9 on the left. There was bilateral papilloedema of 5 to 6 dioptres and punctate retinal haemorrhages. Ocular movements were full and, apart from the deep tendon reflexes which were difficult to obtain, there were no other abnormal physical signs.

Radiographs of the chest and skull were normal. The lumbar C.S.F. pressure was 310 mm. of water, the spinal manometric observations were normal, and the fluid contained 0 cells and 16 mg. of protein per 100 ml. A ventriculogram was normal.

For the next four months she continued to run an intermittent pyrexia of up to 101° F. This was at first attributed to persistence of the mastoiditis and accordingly the left mastoid cavity was re-explored but no abnormality was found. The erythrocyte sedimentation rate (E.S.R.) was above 100 mm. per hour, a white cell count was 13,000 per c. mm., with 73% neutrophils, 14% lymphocytes, 7% eosinophils, and 6% monocytes. The Wassermann reaction and Paul Bunnell test were negative in the blood and C.S.F., agglutinations for *Brucella* were negative, and three blood cultures sterile.

On March 12 she complained of transient attacks of ambylopia. The papilloedema now measured 6 dioptres, the diameters of the blind spots had increased to 40 in. at 2 m., and the visual acuity was J4, 6/18 on the right and J1, 6/9 on the left. The lumbar C.S.F. pressure was 240 mm. of water and the fluid contained 2 polymorphs

per c. mm. and 30 mg. of protein per 100 ml. The haemoglobin was found to be only 43% but this was raised to 85% by transfusion of packed red cells.

In view of the appearances of the optic fundi and the state of vision, it was thought best to do a posterior fossa decompression. On March 18 this was carried out and at operation the dura was tense but there were no other abnormal findings and recovery was uneventful until the second day.

On March 20 she was found to have a moderately severe flaccid weakness of both upper limbs most marked upon the right side. The deep tendon reflexes were absent in the upper limbs, brisk and equal in the lower limbs, and the plantar responses were extensor. No sensory loss was detected at this time, but during the course of the day she developed an almost complete flaccid quadriplegia with total areflexia, loss of vibration and postural sensibility in the fingers and toes, and cutaneous impairment for all modalities of sensation below the level of the third dorsal segment upon both sides. She was incontinent of urine and faeces. A lumbar puncture revealed xanthochromic fluid under a pressure of 150 mm. of water, containing 28 cells per c. mm. (10 polymorphs and 18 lymphocytes), 85 mg. of protein per 100 ml., and a normal sugar. Culture of the C.S.F. was sterile.

By March 22 there was some improvement in power and the sensory level had receded to the level of the tenth dorsal segment. In view of the bizarre clinical picture it was thought that the likely diagnoses included bacterial endocarditis and polyarteritis nodosa, but analysis of the urine was negative and three blood cultures were sterile. The improvement was maintained and on June 22 she was able to move all the limbs against resistance though power was still less than normal. During the two months that had elapsed she had developed global wasting of both hands, but the tendon reflexes had returned and the plantar reflexes were flexor. No cutaneous sensory loss was demonstrable, though the threshold for joint position sense was greater than normal in the fingers and toes upon the right side. Partial sphincter control was effected and, for the first time, the temperature was normal.

By August 20 the papilloedema had subsided, though there was slight pallor of the right optic disc. The visual acuity was J2, 6/12 on the right, and J1, 6/6 on the left. There were no other abnormal physical signs. She was sent to a convalescent home where she gained 2 stones in weight. Since that time she has remained well and the visual acuities have not altered over the last three years.

This patient was considered to have had otitic hydrocephalus. She was given a posterior fossa decompression to preserve vision and, two days later developed a flaccid quadriplegia. It was thought that this complication was due to an extension of intracranial thrombophlebitis to involve veins of the spinal cord.

In five patients there was no evidence of aural suppuration, though there was infection of the respiratory tract. Two patients gave a history of a recent frontal sinusitis which was confirmed by radiological examination. In one of these the sinus infection was a complication of measles and in the other of whooping cough. A further two patients had suffered from a recent attack of acute follicular tonsillitis without abscess formation.

Another unusual case arose in connexion with a lung abscess.

Case 3 (*No.* 19394/41).—Three months before admission to this hospital this patient, a woman aged 33, complained of a generalized headache, coughed up a large quantity of offensive green sputum, and vomited. She was admitted to another hospital where she was found to have a pulmonary abscess with a fluid level in the dorsal segment of the left lower lobe. This was treated with postural drainage and sulphonamides and her symptoms resolved within 14 days. Two months after the onset her headache returned, she complained of diplopia, and began to vomit. She was found to have bilateral papilloedema and, because of the known recent chest infection, the question of a metastatic brain abscess arose.

On examination she was a healthy looking woman of average development and intelligence. The margins of the optic discs were blurred, though there was no measurable swelling. Ocular movements were full and there were no other abnormal signs.

Radiographs of the chest and skull were normal. The lumbar C.S.F. pressure was 180 mm. of water and the fluid contained 0 cells and 35 mg. of protein per 100 ml. A cisternal air encephalogram was normal.

It was considered that her condition arose from thrombosis of an intracranial venous sinus. She received no treatment and the appearances of the optic fundi were normal within six weeks.

Extracranial Venous Thrombosis.—Four patients were known to have had thrombosis of extracranial veins before the onset of intracranial hypertension. In the first two the site of the thrombosis was remote from the jugular system.

Case 4 (*No.* 146716/51).—Nine months before admission, during the fifth month of her second pregnancy, this woman, aged 20, developed swelling of both lower limbs which subsided within three months. Seven months after the onset, three months after parturition, she complained of a slight headache and retired to bed. She vomited twice but, a day later, returned to her household duties. She remained in good health, though a few days afterwards noticed double vision.

On examination she was an obese woman of 5 ft. 3½ in. in height, weighing 12 stones 1 lb. There was bilateral papilloedema of 4 dioptres with a few small retinal haemorrhages. Both external rectus muscles were paralysed and there was a fine nystagmus on lateral gaze to the left. There were no other abnormal physical findings.

Radiographs of the chest and skull were normal. The lumbar C.S.F. pressure was 450 mm. of water, the spinal manometric observations were normal, and the fluid contained 0 cells and 35 mg. of protein per 100 ml. A ventriculogram was normal.

After a further three lumbar punctures she returned home; the squint cleared up within two months and the appearances of the optic fundi were normal at the end of eight months.

It was considered that this patient had developed papilloedema as the result of a venous sinus thrombosis during the puerperium. The association with thrombophlebitis of the lower limbs was presumed from the history. In the following patient there was more definite evidence of extracranial thrombophlebitis.

Case 5 (*No.* 112772/50).—Fourteen months before admission to this hospital this patient, a man aged 41, had a laparotomy on account of swelling of both lower limbs and was found to have a thrombosis of both internal iliac and common femoral veins. Ten months after the operation he developed a moderately severe bifrontal headache. This subsided during the subsequent seven days but, after an interval of a week, headache returned and he began to vomit.

On examination he was an alert man of average development and intelligence, with massive oedema of both lower limbs. There was bilateral papilloedema of 3 to 4 dioptres and punctate retinal haemorrhages. No other abnormal physical signs were detected.

Radiographs of the chest and skull were normal. The lumbar C.S.F. pressure was 300 mm. of water, the spinal manometric observations were normal, and the fluid contained 1 lymphocyte per c. mm. and 80 mg. of protein per 100 ml. A ventriculogram was normal.

A second lumbar puncture was done a week later and the C.S.F. protein was still elevated. He returned home without treatment and remained in good health. The appearances of the optic fundi were normal within one year.

The following two patients are examples of a different kind in whom the internal jugular system was presumed to have been occluded.

Case 6 (*No.* 131941/50).—This woman, aged 30, had had three months previously an operation for the removal of some tuberculous lymphatic glands from behind the angle of the jaw upon the left side. The following day she complained of headache and double vision and was found to have tenderness on palpation over the line of the left internal jugular vein, and local swelling of the neck. Thereafter her vision deteriorated and she was found to have papilloedema.

On examination she was a listless woman, of modest intelligence, who feared that she had incurable tuberculosis. A systolic bruit was heard over the whole cranium and there was bilateral papilloedema of 4 dioptres with punctate retinal haemorrhages. The visual acuities were recorded as J16 on the right, and J14 on the left, but the [illegible] of these findings was in doubt, since there was a hysterical left-sided weakness and hemianaesthesia. A left lower facial weakness was attributed to the operation upon her neck. There were no other abnormal physical signs.

Radiographs of the chest and skull were normal. The lumbar C.S.F. pressure was 300 mm. of water, the spinal manometric observations were normal, and the fluid contained 0 cells and 45 mg. of protein per 100 ml. To exclude a post-operative arteriovenous communication, bilateral carotid arteriograms were done and these were normal.

After a second lumbar puncture she returned home and, though the visual acuities improved to J4 on either side during the next five months, the papilloedema did not subside. She was readmitted and at five lumbar punctures on successive days the C.S.F. pressure was found to be above 300 mm. of water. To avert possible consecutive optic atrophy a subtemporal decompression was done. At operation the dura was so tense that a ventricular tap was contemplated before opening it, but on incising the dura the arachnoid was accidentally nicked and C.S.F. gushed out. The tension on the dura was immediately relieved and it was opened widely. The subarachnoid space was abnormally capacious over the whole field; the cerebral convolutions and cortical veins appeared to be normal. Post-operative recovery was uneventful. Vision was normal within four months, though it was two years before the appearances of the optic fundi were normal. Throughout this period the decompression was not " used ", i.e., it never bulged or became tense.

This patient was presumed to have had thrombosis of the left internal jugular vein following an operation upon the neck. The intracranial hypertension was thought to arise as the result of retrograde extension of the clot into the sagittal sinus. An operative decompression was done to preserve vision.

The second patient in whom occlusion of the internal jugular system seemed to have occurred follows.

Case 7 (*No.* 66223/46).—For the past nine months this woman, aged 32, had been subject to morning headaches which lasted for several hours and were accompanied by vomiting and transient attacks of amblyopia of one or two minutes' duration. During this time her vision deteriorated, and she experienced vertigo, without tinnitus or deafness, which came on at night while she lay in bed. One month previously she had been admitted to another hospital where a ventriculogram was done. It was reported that the findings suggested a left frontal tumour, but after the air studies all her symptoms resolved and she returned home. She was admitted to the Radcliffe Infirmary on September 19, 1939.

On examination she was a healthy looking woman with very markedly distended veins over the chest wall and root of the neck upon both sides (Fig. 1). There was bilateral anosmia* and bilateral papilloedema of 5 to 6

*See footnote on page 33

FIG. 1.—Dilated trunk veins in Case 7, resulting from superior vena cava thrombosis.

dioptres, with punctate retinal haemorrhages. The visual acuity was J6, 6/9 on the right, and J1, 6/9 on the left. No other abnormal physical signs were detected.

The findings suggested the possibility of an olfactory groove meningioma, but radiographs of the skull were normal. The lumbar C.S.F. pressure was 460 mm. of water and there was no rise when either or both internal jugular veins were compressed. The C.S.F. contained 0 cells and 20 mg. of protein per 100 ml. A ventriculogram was normal.

She returned home, but the papilloedema did not subside, and she was readmitted on April 19, 1940. The following day a subtemporal decompression was done. At operation the dura was very tense and, when this was incised, the membrane of a small chronic subdural haematoma was revealed. The membrane was no more than 2 to 3 mm. in thickness ; it was considered that this bore little relation to her present condition and probably arose as a complication of the first ventriculogram. After operation there was a temporary improvement of vision, but this was not sustained. Radiographs of the chest failed to show any evidence of a mediastinal neoplasm, and it was felt that her condition was due to thrombosis of the superior vena cava.

During the following three months she developed bilateral pleural effusions, ascites, hepatic enlargement, oedema of the lower extremities, and enormous distension of the decompression. These were treated by repeated aspirations and lumbar puncture, with some effect. In 1946 her visual acuity was J14, 6/18 on the left, and perception of light only on the right. She started to have major convulsions, but these were partially controlled with anticonvulsants. She was last seen in 1951, when she was technically blind.

Cases Associated with Obesity.—It is not uncommon to find a moderate elevation of the lumbar C.S.F. pressure in an obese but otherwise healthy person. This is due to the pressure exerted by the thighs and abdominal fat upon the lumbar veins when the patient is in the lateral position usually employed for spinal puncture. The presence of papilloedema, however, cannot be so lightly dismissed and, in this series, six patients gave a history of a rapid increase in weight and were found to be obese. In four of these there was no other cause to account for the intracranial hypertension, though of the other two, one had mitral stenosis and one gave a history of a miscarriage eight months before admission to hospital. It will also be remembered that Case 4 (see p. 31) was obese, although her clinical state seemed more probably due to postpartum venous thrombosis.

Case 8 (*No.* 44996/45).—This woman, aged 36, had gained 3½ stones in weight in the past two years. Eighteen months before admission her menses became irregular, lasting for five days and following a cycle of from two to eight weeks. One year before admission she started to have mild morning headaches and six months later noticed progressive failure of vision.

On examination she was an obese woman of 5 ft. 4 in. in height weighing 13 stones 10 lb. There was bilateral papilloedema of 2 dioptres. The visual acuities were preserved and, apart from a fine horizontal nystagmus on lateral gaze, there were no other abnormal findings.

Radiographs of the chest and skull were normal. The lumbar C.S.F. pressure was 280 mm. of water, the spinal manometric observations were normal, and the fluid contained 0 cells and 20 mg. of protein per 100 ml. A ventriculogram was normal.

She received no treatment and became symptom free after one week ; the appearances of the optic fundi were normal within one month.

Two similar patients included B. W. (No. 72041/47), a woman aged 25 who was 5 ft. 6 in. in height and weighed 14 stones ; and V. D. (No. 6442/41), a woman aged 42, who was 5 ft. 6½ in. in height and weighed 15 stones 7 lb. Both of them gave a history of a recent rapid gain in weight in the two years before admission and were found to have three dioptres of papilloedema. There were no other abnormal findings and analysis of the lumbar C.S.F., radiographs of the chest and skull, and a ventriculogram were normal.

There was only one male in this group, a boy who appeared to be suffering from a mild hypothalamic disorder.

Case 9 (*No.* 134418/52).—This boy, aged 12, had been normal up to the age of 11 when he gained 2 stones 5 lb. in weight within nine months and became apathetic. He slept late if not awakened, but there was no diurnal

* A similar case is under observation at present : a healthy young man, with bilateral anosmia, intense papilloedema, slight mental changes, all suggesting the possibility of an olfactory groove meningioma. Bilateral carotid angiograms and a ventriculogram are quite normal and are presumed to exclude the presence of a tumour.

sleep and his fluid balance was normal. One year before admission he began to complain of throbbing headaches which were at times sufficiently severe to keep him from school. For the past three months he had been subject to episodes of vertigo, without deafness or tinnitus, which lasted for up to two hours at a time.

On examination he was an apathetic fat boy of 5 ft. 4 in. in height who weighed 11 stones 5 lb. The external genitalia were of average development for his age, the pubic hair was sparse, and the fingers tapering. There was bilateral papilloedema of 1 to 2 dioptres and the ankle jerks were absent. No other abnormalities were detected.

Radiographs of the chest and skull were normal. The lumbar C.S.F. pressure was 290 mm. of water, the spinal manometric observations were normal, and the fluid contained 0 cells and 25 mg. of protein per 100 ml. A lumbar air encephalogram was normal ; in particular, the regions of the sella and the third ventricle were clearly visualized and were not remarkable.

After a second spinal puncture he returned home and when seen three months later seemed much brighter and the appearances of the optic fundi were normal. Three years later he was head boy of his school, played active games and was in every respect normal. He weighed 14 stones 2 lb. We have no explanation for the spontaneous recovery from both an endocrine condition and intracranial hypertension.

Of the two patients that remain in this group, one gave a history of a miscarriage, the other had hypertension and mitral stenosis. Barnett and Hyland (1953) have shown that each of these conditions may be associated with cortical thrombophlebitis, so that it is not possible to relate the intracranial hypertension to obesity alone. However, the clinical picture most closely resembled that of sinus thrombosis as distinct from cortical thrombophlebitis.

Case 10 (*No.* 152302/52).—After the birth of her first child, two and a half years previously, this woman, aged 22, had gained 3 stones in weight. Eight months before admission she had a miscarriage during the tenth month of pregnancy. A week later she complained of headache, vomited, and developed diplopia. While awaiting admission her symptoms subsided spontaneously.

On examination she was an obese woman of 5 ft. 6 in. in height who weighed 13 stones. There was bilateral papilloedema of 3 dioptres on the left and 5 dioptres on the right. No other abnormality was detected.

Radiographs of the skull showed slight decalcification of the posterior clinoid processes and of the dorsum sellae. The lumbar C.S.F. pressure was 400 mm. of water, the spinal manometric observations were normal, and the fluid contained 0 cells and 35 mg. of protein per 100 ml. A ventriculogram was normal.

She was given no treatment and the appearances of the optic fundi were normal within 16 months.

Case 11 (*No.* 66066/46).—This patient, a woman aged 39, had had rheumatic fever at the ages of 20 and 23, and 11 weeks before admission had a third attack characterized by a pyrexia of up to 100° F., flitting large joint pains, and profuse perspiration. After eight weeks in bed she complained of a sensation of pressure behind the eyes and deterioration of vision.

On examination she was an obese woman of 5 ft. 2 in. in height who weighed 13 stones 3 lb. There was bilateral papilloedema of 5 to 6 dioptres with retinal exudates and haemorrhages. Visual acuity was reduced to perception of light on the right and J14, 6/12 on the left. The blood pressure was 160/110 mm. Hg and at the cardiac apex there was a mitral diastolic murmur. The pulse was regular and there were no other abnormal physical signs.

A radiograph of the chest showed evidence of mitral stenosis. Radiographs of the skull revealed slight decalcification of the dorsum sellae and of the posterior clinoid processes. The lumbar C.S.F. pressure was 400 mm. of water, the spinal manometric observations were normal, and the fluid contained 0 cells and 40 mg. of protein per 100 ml. A ventriculogram was normal.

Four lumbar punctures were done and after four months the papilloedema measured 2 dioptres. The visual acuity was J6, 6/12 on the right and perception of light on the left. Two years later the swelling had subsided and the vision was unaltered.

Post-traumatic Cases.—Two patients developed papilloedema after a closed head injury.

Case 12 (*No.* 156126/52).—Ten days before admission this boy, aged 6, sustained a mild closed head injury with a post-traumatic amnesia of 10 minutes. The following morning he complained of severe headache and vomited.

On examination he was a quiet little boy with a bony depression over the left parietal region of the vault. There was bilateral papilloedema of 2 to 3 dioptres with a few small retinal haemorrhages. No other abnormality was detected.

Radiographs of the skull showed a depressed fracture, 3 cm. in diameter and 2 cm. in depth, in the left parietal region bordering on the midline. This was elevated at operation and the dura was found to be intact. Within two weeks the appearances of the optic fundi were normal and he was well. The site of the depressed fracture suggested that the sagittal sinus had been damaged.

In the second case a mural thrombosis of the superior longitudinal sinus was inferred from the results of sinography.

Case 13 (*No.* 134418/50).—A man, aged 38, eight months before admission sustained a closed head injury without loss of consciousness. Seven months later he complained of occasional left-sided headaches and double vision.

On examination there was a large vitreous haemorrhage in the left eye and bilateral papilloedema of 1 to 2 dioptres. The visual acuity was J4, 6/18 on the left, and J4, 6/9 on the right. Both external rectus muscles were paralysed. No other abnormal physical signs were detected.

Radiographs of the skull showed slight decalcification of the dorsum sellae. The lumbar C.S.F. pressure was 180 mm. of water and the fluid contained 0 cells and 20 mg. of protein per 100 ml. A lumbar air encephalogram was normal. Through a frontal burr-hole, 10 ml. of "thorotrast" was injected into the sagittal sinus. The lumen of the sagittal sinus seemed to be attenuated and the walls irregular: the lateral sinus was normal.

He returned home without treatment. The appearances of the optic fundi and the left vitreous were normal within one year when the visual acuity was J1, 6/6 on either side.

Cases of Undetermined Origin.—There remain four patients in whom no obvious cause was found to account for their papilloedema. Two of these were women aged 18 and 20 and the clinical features closely resembled those which have been described. The third, Case 15, is reported later (q.v.), whilst the fourth follows.

Case 14 (*No.* 16904/43).—This patient, a woman aged 20, was a dwarf who was mentally backward. A year before admission she had been investigated for anaemia. In short, this was microcytic and hypochromic in type and had proved refractory to treatment with oral iron and intramuscular liver. Both a glucose tolerance test and a fat balance suggested impairment of intestinal absorption and it was considered likely that absorption of haematinic factors was also defective. Two months before admission she complained of headache and double vision.

On examination she was a well proportioned dwarf of 4 ft. 9½ in. in height who weighed 5 stones 5½ lb. and was mentally backward. The face was pigmented, the genitalia infantile, and pubic hair sparse. Veins over the forehead were prominent and there was bilateral papilloedema of 5 to 6 dioptres. Both external rectus muscles were paralysed and the deep tendon reflexes difficult to obtain. The blood pressure was 100/70 mm. Hg and no other abnormal physical signs were detected.

Radiographs of the skull revealed a very small pituitary fossa. The lumbar C.S.F. pressure was 210 mm. of water and the fluid contained 2 lymphocytes per c. mm. and 10 mg. of protein per 100 ml. A ventriculogram showed slight dilatation of otherwise normal ventricles.

She received no treatment for the intracranial hypertension and the appearances of the optic fundi were normal after two weeks. It was considered that the papilloedema arose from a sinus thrombosis and that this may have been associated with the anaemia.

Symptoms and Physical Signs

The incidence of the symptoms and physical signs is shown in Tables III and IV.

A striking feature was the rarity of constitutional symptoms. Only five patients complained of malaise, and this was related more to the predisposing infection than to the raised intracranial pressure. Only one patient (Case 3) was really ill and this was a most unusual case.

TABLE III
SYMPTOMS

Symptom	Total	Group 1	Groups 2–5
Constitutional	5	4	1
Headache	30	16	14
Vomiting	17	11	6
Visual deterioration	11	3	8
Squint and/or diplopia	26	21	5
Fits	5	3	2
Total number of cases	42	26	16

TABLE IV
PHYSICAL SIGNS

Physical Sign	Total	Group 1	Groups 2–5
Enlargement of head circumference	11	10	1
Papilloedema of > 3 dioptres	13	7	6
Papilloedema of < 3 dioptres	29	18	11
Visual acuity of J2, 6/9–J6, 6/12	9	4	5
Vision worse than J6, 6/12	6	2	4
External rectus weakness Total	26	22	4
Unilateral	8	8	0
Bilateral	18	14	4
Sluggish or absent tendon jerks	11	6	5
Nystagmus	9	5	4
Slight facial weakness	4	3	1
Monoplegia	1	1	0
Hemiplegia	1	1	0
Bruit audible over the cranium	2	1	1

Headache.—Headache was seldom a troublesome symptom and this was especially true of the otitic group. It was particularly uncommon in children and, of the 15 patients under the age of 12, only five admitted to a mild headache.

Though headache is so slight in these patients there is usually abundant evidence of raised intracranial pressure. There is papilloedema, elevation of the spinal fluid pressure, and separation of the cranial sutures sometimes evident on clinical examination by a cracked-pot note to percussion or by an increase in the head circumference. Radiologically there may be suture diastasis or convolutional thinning of the vault. Eleven of the 15 children showed these changes in the skull radiographs. Admittedly children are loth to complain, but when the same clinical and radiological findings are due to, say, a cerebellar tumour, headache is a common symptom and may be the predominant one. Nor is the absence of headache to be explained on the basis of a time relationship, because the increase in pressure may develop as slowly or as quickly in cases of brain abscess or tumour. In these 11 children the duration of symptoms before examination was from 10 days to six months, with an average of 12 weeks.

Possible factors which may be relevant are that there is rarely any great ventricular dilatation (as in obstructive hydrocephalus due to a cerebellar

tumour) nor is there any lateral shift or distortion of the cranial contents.

In the whole series only one patient described his headache as violent.

Case 15 (*No.* 189205/54).—A man, aged 33, two years previously began to complain of mild bifrontal headaches of a few minutes' duration. Five weeks before admission he started to have attacks of sudden and very severe headache associated with rotatory vertigo and ambylopia. These episodes lasted for up to five minutes and recurred five or six times a day. Between the attacks he enjoyed good health.

On examination he was a healthy looking man without evidence of psychoneurosis. There was bilateral papilloedema of 5 to 6 dioptres and the visual acuities were J4, 6/12. Apart from a slight left lower facial weakness, no other abnormal signs were detected.

Radiographs of the skull showed slight thinning of the posterior clinoid processes and decalcification of the dorsum sellæ. A right carotid arteriogram was normal. It was considered that the history and absence of focal signs suggested intermittent ventricular obstruction, as from a colloid cyst of the third ventricle, and a ventriculogram was done. The intraventricular pressure was 650 mm. of water and the fluid contained 90 red cells per c. mm., 0 white cells, and 35 mg. of protein per 100 ml. Air studies were normal.

In the light of these findings it was thought that his condition was closely related to otitic hydrocephalus and, because of the attacks of ambylopia, he was given a subtemporal decompression. At operation there were no abnormal findings. During the next few weeks he became symptom free and visual acuity improved to J2, 6/6 on either side. Eight months later there were still 2 dioptres of papilloedema though he remained well.

Vomiting.—This was a fairly frequent occurrence, especially in children, but it was rarely so insistent as in patients with intracranial hypertension from brain tumour. When present it was usually a feature of the associated acute infection. None of these patients exhibited lethargy or sleepiness so commonly seen in raised intracranial pressure from other causes. Indeed, their alacrity and general well being in the presence of marked papilloedema was often characteristic and came to be recognized as being of diagnostic importance.

State of Vision.—As papilloedema was the essential feature of all these cases, and the one which led to admission to hospital, our interest has been centered on the state of vision. In most instances the patient had no symptom referable to the papilloedema, although a few with high degrees of swelling experienced transient attacks of ambylopia. Gross impairment of vision in the acute stage or later as the result of consecutive optic atrophy was rare (Table IV), and of the whole series only two patients became blind. One of these (Case 7) has been described ; the other follows.

Case 16 (*No.* 182095/53).—A boy, aged 5, four weeks before admission developed a squint and, after one week, was taken to see an ophthalmologist who reported that the visual acuities and appearances of the optic fundi were normal. After a few days he was found to have a non-suppurative left otitis media but this cleared up within three days. A week before admission he began to walk into the furniture and, for the first time, it was suspected that his vision was defective. He remained otherwise in excellent health.

On examination the head circumference was 22½ in. and there was a cracked-pot note to percussion. Veins over the forehead were prominent and a systolic bruit was heard over the whole cranium. There was bilateral papilloedema of 5 to 6 dioptres with retinal haemorrhages and macular fans of exudate. The left eye was blind and acuity on the right was reduced to perception of light. Both pupils were inactive to light and there were bilateral sixth nerve palsies. The deep tendon reflexes were all difficult to obtain but there were no other abnormal physical signs.

Radiographs of the skull showed moderate suture diastasis and increased convolutional markings. The lumbar C.S.F. pressure was 470 mm. of water, the manometric observations were normal, and the fluid contained 0 cells and 40 mg. of protein per 100 ml. A ventriculogram was attempted, but the ventricles were difficult to locate and failed to fill with air. In order to try to save vision a subtemporal decompression was done. At operation, the scalp veins were distended and black. The dura was tense and, when the arachnoid was incised, C.S.F. gushed out from a capacious subarachnoid space. The cerebral convolutions appeared to be normal but the cortical veins were widened, tortuous, and filled with dark blood. Serial lumbar punctures showed that the pressure was normal within one week. A lumbar air encephalogram four weeks later showed slight dilatation of otherwise normal ventricles. He returned home blind but in good health. He did not "use" the decompression and four months later had bilateral consecutive optic atrophy.

The rapid development of papilloedema and visual failure suggested obstruction to the venous return from the eyes.

Diplopia.—Diplopia was another common symptom and was due in every instance to paralysis of one or both external rectus muscles. Twenty-one of the 26 patients with sixth nerve palsies fell into Group 1 (19 otitic), and, of these, 12 were bilateral and nine unilateral. In eight of the latter the localization was upon the same side as the aural suppuration. The frequency with which the sixth nerve is singled out is remarkable and may have aetiological significance. Symonds (1952) has suggested that the sixth nerve is compressed by an accretion of clot in the inferior petrosal sinus. In all patients the sixth nerve palsy cleared up long before the papilloedema resolved and both the transient duration and lateralization lend support to the theory of a compressive lesion.

Convulsions.—Five patients had one or more convulsions. Of these, one was a known epileptic and another had a fit at the height of an acute mastoid infection. Two of the remainder had, in addition, focal signs : one a weakness of the left upper limb, the other a mild right hemiplegia. Since fits and focal signs are common in cortical thrombophlebitis, it is probable that the occurrence of convulsions bespoke an extension of the thrombotic process into the cerebral veins as opposed to the sinuses.

The Cerebrospinal Fluid

With the exception of one patient (Case 12), all had one or more lumbar punctures. Generally speaking, great elevation of the spinal pressure was not common, and usually it was considerably less than the appearances of the optic fundi would have led one to expect. The initial pressures, measured in mm. of water, were 60 to 180 (three cases), 181 to 300 (24 cases), and greater than 300 mm. (14 cases).

Separate compression of the left and right internal jugular veins was done in 33 patients and the manometric observations were normal in 26. In six patients there was evidence of obstruction to the internal jugular vein or transverse sinus upon one side, whilst in one (Case 7) bilateral jugular compression failed to effect a rise of the spinal C.S.F. pressure.

The protein content of the lumbar C.S.F., measured in mg. per 100 ml., was 10 to 25 (29 cases), 26 to 50 (10 cases), and greater than 50 (two cases). Six patients had a cell count of more than 3 lymphocytes per c. mm. Thus the lumbar C.S.F. was abnormal in seven patients, but, of these, two had had a ventriculogram before analysis of the fluid. Table V shows the nature of the abnormalities found in the remaining five patients.

TABLE V
PRE-OPERATIVE ABNORMALITIES OF THE C.S.F. IN FIVE CASES

Cells (per c.mm.)	Protein (mg. per 100 ml.)
1 lymphocyte	80 (Case 5)
38 ,,	90
12 ,,	20
11 ,,	25
0 ,,	52

Three of the patients were lumbar punctured within a few days of an acute mastoid infection, and one within five days of acute follicular tonsillitis. Each patient was submitted to a second lumbar puncture after five to seven days when, in every instance, the fluid was normal. Case 5, which has been described, had been immobilized in bed for several months and this may possibly have accounted for the elevation of the C.S.F. protein.

Thus it appears that during the acute stage of infection the presence of a moderate pleocytosis or elevation of the protein of the lumbar C.S.F. does not exclude a diagnosis of otitic hydrocephalus. In general summary, analysis showed the following :

(1) The pressure, though elevated, is not so high as the degree of papilloedema would suggest.

(2) Evidence of a major sinus occlusion by jugular compression is often absent.

(3) The fluid usually has a normal, or lower than normal, protein content.

(4) There is usually no cellular reaction.

This information is of great value in the differentiation between otitic hydrocephalus and brain abscess. Since well over 90% of patients with brain abscess show an increase in the cellular or protein content (or both), the finding of a normal C.S.F. considerably weights the evidence in favour of otitic hydrocephalus.

Ventricular Air Studies

Air studies were attempted by the ventricular, cisternal, or lumbar routes upon 32 patients. In 31 the ventricles were symmetrical with free intercommunication ; in one they seemed to be small and could not be filled. In 18 the findings were entirely normal. In four the ventricles were small and looked " pinched " (Fig. 2), and in all of these

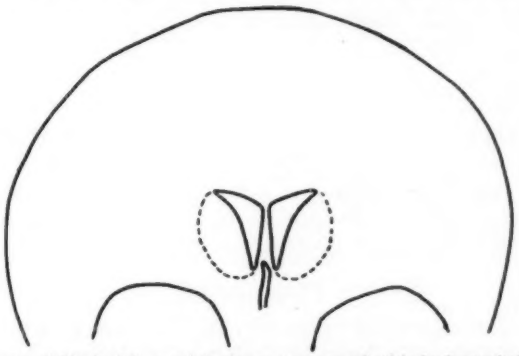


FIG. 2.—" Pinched " ventricles in acute stage of otitic hydrocephalus.

patients there was a history of less than five weeks. The appearances of the ventricles suggested that they were subjected to an evenly dispersed pressure, as from distension of the subarachnoid space in the region of the vertex.

In nine patients there was a slight uniform dilatation of the ventricles (Fig. 3), and this also occurred after operation in Case 16. All of these patients had air studies more than six weeks after the onset of symptoms, the average time interval being 15 weeks.

From these findings it appears that the size of the ventricles is related to the duration of symptoms

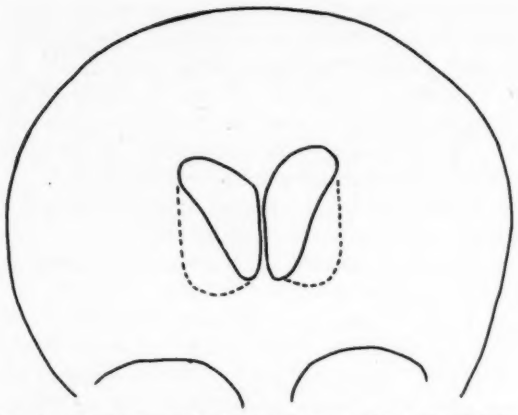


FIG. 3.—Dilated ventricles in late stage of otitic hydrocephalus.

before air encephalography and this may explain the diverse reports of others. In any case the ventriculogram is usually sufficient to exclude a space-occupying lesion.

Other Investigations

Sinograms were done on four patients ; in two, attempts to fill the sagittal sinus failed although the needle was demonstrated within the sinus by radiography. In the other two the findings suggested a mural thrombosis of the sagittal sinus. This method of investigation proved disappointing, and it must be emphasized that none of the results was unequivocal.

Unilateral carotid arteriography was done on four patients, and bilateral on two. This served to exclude a space-occupying lesion in three patients who did not have air studies. Apart from " bowing " of the anterior cerebral arteries, presumably due to slight ventricular dilatation, no abnormality was detected either in the arterial or venous phase.

Management

The immediate problem in the management of these patients is the exclusion of a space-occupying lesion and, as stated above, analysis of the C.S.F. may provide valuable information. Almost always, however, a ventriculogram or an arteriogram is necessary to confirm the diagnosis.

When this has been done the question of treatment arises. The alternatives which have been suggested are to reduce the C.S.F. pressure by repeated spinal puncture, or to proceed straight away to an operative decompression. We have found the first ineffective and the second rarely necessary and, in the majority of our patients, no treatment was given. A few patients were submitted to repeated spinal puncture for interest, and it was found that the pressures fluctuated widely from day to day. An example is shown in Fig. 4. In other cases the removal of 10 to 15 ml. of C.S.F. twice daily failed to effect a sustained fall of pressure.

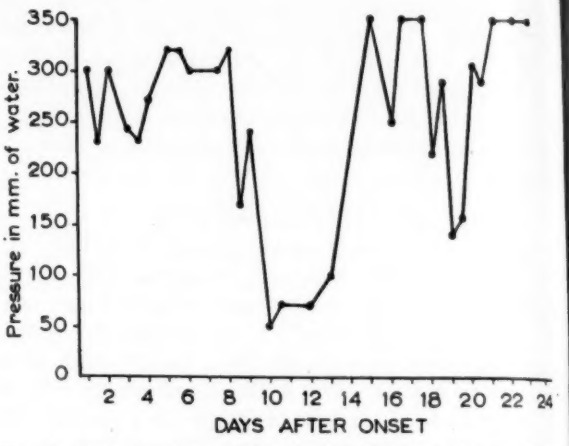


FIG. 4.—Chart showing variations in C.S.F. pressure at daily lumbar punctures.

In short, 15 patients had three or more lumbar punctures, but we found no evidence that they influenced the recession of the papilloedema in any way. Whether or not repeated spinal punctures were employed, there was an average period of seven months before the appearances of the optic fundi returned to normal. It would also appear that frequent spinal puncture will not prevent consecutive optic atrophy, for one patient, who had had over 20, was left with perception of light only in one eye and a visual acuity of J6, 6/9 in the other.

The indications for operative decompression were significant reduction of vision, severe and persistent papilloedema and, in one patient (Case 15), paroxysmal headache which was thereby relieved. But it was by no means always successful in preserving vision and, of the six patients who had an operative decompression to avert blindness, two became blind (Cases 7 and 16), one had good vision in one eye preserved, and three recovered normal visual acuity ; they might, of course, have done so without a decompression.

One patient came to operation for a different reason ; she was thought to have a posterior fossa tumour.

Case 17 (*No.* 28130/52).—A girl, aged 4, five months previously was treated with penicillin for a left otitis media. This resolved after 10 days when she developed a squint. She was admitted to another hospital where she was found to have papilloedema and subsequently transferred to the Radcliffe Infirmary with a diagnosis of a posterior fossa tumour.

On examination she was a healthy looking child with bilateral papilloedema of 3 to 4 dioptres. No other abnormality was detected.

Radiographs of the skull showed gross suture diastasis. A right occipital burr-hole was made and a needle inserted into the lateral ventricle. The pressure was 500 mm. of water and the ventricle appeared to be capacious. It was decided to proceed to a posterior fossa exploration without preliminary air studies. When the dura was incised, the occipital sinus was found to measure 2 cm. in width and to be distended with dark blood. No other abnormality was detected. The child remained well and the appearances of the optic fundi were normal within six months.

All the evidence, in retrospect, pointed to an otitic hydrocephalus which was probably due to thrombosis of the right transverse sinus.

In one patient a parieto-occipital decompression was done to provide an opportunity for studying the intracranial venous sinuses.

Case 18 (*No.* 38685/45).—A boy, aged 5, three months before admission had a myringotomy for an acute left-sided suppurative otitis media. Nine weeks later he developed a streptococcal arthritis of the left hip and a squint. The arthritis subsided after penicillin treatment and he was transferred to the Radcliffe Infirmary.

On examination there was bilateral papilloedema of 5 dioptres with retinal haemorrhages and exudates. The right external rectus muscle was paralysed but there were no other abnormal physical signs; in particular the left hip was clinically and radiologically normal.

Radiographs of the skull showed slight suture diastasis. The lumbar C.S.F. pressure was 260 mm. of water and the fluid contained 1 lymphocyte per c. mm. and 20 mg. of protein per 100 ml. There was no rise of this pressure when the left jugular vein was compressed; on the right side the spinal manometric observations were normal. Since he was having amblyopic attacks a decompression was done.

A left-sided osteoplastic flap was turned to expose the posterior part of the sagittal sinus, the torcula, the left transverse sinus, and the genu. The posterior 2 cm. of the sagittal sinus and the beginning of the right lateral sinus appeared normal. From thence forwards, for about 4 cm., the sagittal sinus was quite flat, on the same plane as the dura, and the surface was reddened. Anterior to this the normal convexity of the sinus reappeared, although the surface was granular and pink. The left transverse sinus was also flat, reddened, and granular as far as the genu. A hollow needle was inserted into the flattened portions of the sinuses and, in all positions, there was a free flow of blood through it, showing that the lumen was patent. When the dura was opened it was apparent that there was an excess of C.S.F. around the Pacchionian granulations and, after the arachnoid had been pricked, C.S.F. gushed out under increased pressure from a capacious subarachnoid space. The cerebral convolutions and cortical veins appeared to be normal.

He was discharged from hospital after two weeks and remained well. The decompression neither bulged nor became tense and the appearances of the optic fundi were normal after seven months.

These observations suggested a mural thrombosis of the left transverse and sagittal sinuses which did not amount to complete occlusion.

Of the patients who came to operation, only two seemed to "use" the decompression. In none of the frankly otitic cases did it seem to serve any useful function.

Discussion and Conclusions

The label "otitic hydrocephalus" for these cases is clearly unsuitable, since infections of the second branchial cleft are not exclusive in the production of the syndrome. In the present series, for instance, 21 of the 42 cases were in no way "otitic". Moreover, most clinicians in speaking of hydrocephalus imply dilatation of the cerebral ventricles and, as has been shown, this is not a feature of otitic hydrocephalus. In the absence of a fuller understanding of the pathogenesis it is best to avoid a designation which carries aetiological implications, and it is proposed to employ the term "benign intracranial hypertension".

In 10 patients there was reason to infer obstruction to the venous outflow from the cranium, as low down as the superior vena cava (Case 7), or as high up as a major intracranial venous sinus. Thus, in six patients, compression of the jugular vein upon one side, and in one upon both sides, failed to effect a rise of the spinal C.S.F. pressure. In addition, the lateral sinus was reported to have been thrombosed in two patients who had had a mastoidectomy, and in another (Case 17) the occipital sinus was dilated suggesting occlusion of the transverse sinus.

Obstruction to the jugular system might, as Symonds (1952) has suggested, give rise to oedema of the brain or to increased secretion of C.S.F. Indeed, either of these mechanisms would explain the presence of small ventricles in the acute stage of the condition. However, cerebral oedema is most often associated with marked constitutional symptoms and focal signs (as in hypertensive encephalopathy and brain abscess) which are not found in benign intracranial hypertension. It will also be remembered that in three patients who had a decompression the subarachnoid space was capacious, a finding incompatible with cerebral oedema. For these reasons we believe that the clinical picture and size of the ventricles are caused by an

excess of C.S.F. over the convexity of the hemispheres.

If there is no evidence of occlusion to the jugular system, it is still possible, as Symonds pointed out, that a mural thrombus which does not impair the lumen may exist in relation to the arachnoid villi and thereby impede the reabsorption of C.S.F. We have seen patients with small ventricles and papilloedema consequent on subarachnoid haemorrhage and it is possible that debris of red blood cells may act in a similar way. Without necropsy material it has rarely been practicable to prove or refute this theory. However, in six patients in this series it was possible to invoke thrombosis of the sagittal sinus. Four patients had sinograms and the findings suggested total occlusion in two and a mural thrombosis in two. The operative observations in Case 16 of dilated scalp and cortical veins led us to infer obstruction to the sagittal sinus, whilst in Case 20 the posterior portions of the sagittal and transverse sinuses were flat, reddened, and granular.

The benign nature of the process is also compatible with a thrombosis. The discovery of papilloedema often causes alarm and in the acute phase of the illness there may be some headache, but this is usually short-lived. In the chronic stage during which the papilloedema is resolving the patient may seem to be perfectly well. The onset presumably bespeaks the actual incidence of thrombosis, and later the absorption of C.S.F. is probably re-established either by the original channels or by new ones.

This condition is closely related to cortical thrombophlebitis, which, however, calls attention to itself by gross evidence of hemisphere dysfunction, e.g., fits, hemiplegia, aphasia, hemianopia, etc. Usually there is no papilloedema, but we have seen cases in which, during or after resolution of the focal signs, papilloedema developed, presumably due to a spread of the thrombotic process to the sinuses from the cerebral veins. Similarly, we have observed patients with benign intracranial hypertension develop focal signs, which suggests an extension of the thrombosis from the sinuses to involve cortical veins. In both groups, spontaneous recovery usually occurs.

In 26 patients there was no direct evidence of thrombosis of intracranial sinuses or veins, although two sustained a head injury in the region of the sagittal sinus and a post-traumatic thrombosis of this structure was suspected. A further patient (Case 6) gave a history strongly suggestive of a thrombosis of the left internal jugular vein which followed an operation upon the neck. Indirect evidence was provided in 35 of the 42 patients by the history or detection of conditions known to be associated with intracranial venous thrombosis. These included infections of the second branchial cleft (21), acute follicular tonsillitis (two), frontal sinusitis (two), trauma (two), mitral stenosis (one), and anaemia (one). In addition, two cases arose in connexion with pregnancy and, including one of these, four patients had evidence of extracranial venous thrombosis. A particularly unusual case has been described in which papilloedema developed in association with a lung abscess. In seven patients there was no well recognized cause to explain the syndrome.

The six patients who were obese formed an interesting group, as the gain in weight seemed closely related to the onset of raised intracranial pressure. With one exception, a boy who appeared to have a mild hypothalamic disorder, all these patients were women. It will also be remembered that two of the three patients with no associated pathology who were included in Group 5 were women. This suggests that endocrine factors may be concerned in the balance between the secretion and reabsorption of the C.S.F., but in what fashion remains obscure. That endocrine disorders can influence the composition of the C.S.F. has been shown by Thompson, Thompson, Silveus, and Dailey (1929) who found an increase in the protein content of the C.S.F. in 13 of 17 patients with myxoedema, whilst Jefferson (1956) noted the appearance of papilloedema in patients with Addison's disease.

Since this paper was started a notable contribution has been made by Foley (1955) who has reviewed 166 patients, including 60 personal cases, with intracranial hypertension. Fifty-nine of these were associated with aural suppuration and the clinical findings are similar to those of the " otitic " group herein described. In a further number of Foley's patients it was possible to incriminate a pre-existing extracranial infection or a head injury. However, in 31 of his personal cases no obvious cause was found. The ratio of females to males in this group was 2 : 1 and it is of particular interest that 22 of the women were obese. Thus, in two independent series, analysis has revealed a group of undetermined aetiology, possibly related to endocrine dysfunction, which is worthy of further study.

Most authorities, including Symonds (1931), Garland and Seed (1933), and Garcin and Pestel (1949), have recommended repeated spinal puncture to avert the development of consecutive optic atrophy. Others have preferred to do an operative decompression. Evidence has been presented to

show that the first is ineffective and the second usually unnecessary, and most of our patients received no treatment. The duration of the papilloedema is often a matter of months, though it may persist for as long as two years ; in either instance, the eventual outcome is almost always satisfactory. For the occasional patient with a high degree of papilloedema which does not subside under observation, who has significant visual failure or attacks of ambylopia, it is probably best to do a decompression. By this means everything has been done to preserve vision, though it must be admitted that these patients do not often " use " the decompression.

Summary

Forty-two patients with papilloedema, unrelated to brain tumour or other well defined cause, are reviewed.

Five clinical groups were distinguishable by reason of an associated pathology : (1) Infections of the second branchial cleft and respiratory tract (26 cases) ; (2) extracranial venous thrombosis (four cases) ; (3) obesity (six cases) ; (4) post-trauma (two cases) ; (5) undetermined (four cases).

Headaches and other symptoms of increased intracranial pressure were usually slight in proportion to the papilloedema.

Strabismus and diplopia were common and were always due to paralysis of one or both external rectus muscles.

Visual failure was rare, despite the persistence of papilloedema for many months.

Fits and focal signs were rare, and their occurrence is thought to indicate thrombosis of cortical veins.

The lumbar spinal fluid pressure, although usually elevated, was not as high as the degree of papilloedema would lead one to expect.

The spinal fluid was usually normal, although the protein content was frequently lower than normal.

Confirmation of the diagnosis is essential, and this usually entails ventriculography. In the acute stage the ventricles may be slightly smaller than normal, but later may be slightly dilated.

Treatment by repeated lumbar puncture was ineffective. In cases of impending visual failure, decompression operations may be called for.

I wish to thank Mr. J. Pennybacker for his valuable advice and encouragement in the preparation of this paper, and for allowing me to examine the case records and patients admitted under his care.

References

Bailey, O. T., and Hass, G. M. (1937). *Brain*, **60**, 293.
Barnett, H. J. M., and Hyland, H. H. (1953). *Ibid.*, **76**, 36.
Davidoff, L. M., and Dyke, C. G. (1936). *J. nerv. ment. Dis.*, **83**, 700.
Ellis, R. W. B. (1937). *Proc. roy. Soc. Med.*, **30**, 768.
Foley, J. (1955). *Brain*, **78**, 1.
Frenckner, P. (1937). *J. Laryng.*, **52**, 350.
Garcin, R., and Pestel, M. (1949). *Thrombo-phlébites cérébrales.* Masson, Paris.
Garland, H. G., and Seed, G. S. (1933). *Lancet*, **2**, 751.
Jefferson, A. (1956). *Journal of Neurology, Neurosurgery and Psychiatry*. **19**, 21.
Kendall, D. (1948). *Brain*, **71**, 386.
Martin, J. P., and Sheehan, H. L. (1941). *Brit. med. J.*, **1**, 349.
McKenzie, W. (1948). *J. Laryng.*, **62**, 391.
McAlpine, D. (1937). *Brain*, **60**, 180.
Nielsen, J. M., and Courville, C. B. (1934). *Ann. Otol. (St. Louis)*, **43**, 972.
Pennybacker, J. (1943). *Trans. ophthal. Soc. U.K.*, **63**, 333.
Sugarbaker, E. D., and Wiley, H. M. (1951). *Cancer*, **4**, 242.
Symonds, C. P. (1931). *Brain*, **54**, 55.
——(1932). *Brit. med. J.*, **1**, 53.
——(1937). *Brain*, **60**, 531.
——(1940). *Brit. med. J.*, **2**, 348.
——(1952). *Ann. roy. Coll. Surg. Engl.*, **10**, 347.
Thompson, W. O., Thompson, P. K., Silveus, E., and Dailey, M. E. (1929). *Arch. intern. Med.*, **44**, 368.
Weed, L. H. (1914). *J. med. Res.*, **31**, 51.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 42.

HYPEROSTOSIS FRONTALIS INTERNA

BY

S. SMITH and R. E. HEMPHILL

From Barrow Hospital, Barrow Gurney, near Bristol

It was in 1765 that Morgagni first described the triad of hyperostosis frontalis interna, obesity, and virilism. More than 150 years later Stewart (1928) and Morel (1930), on examining hyperostosis frontalis interna in psychiatric cases, suggested that the combination of hyperostosis and endocrine and neuropsychiatric disturbances was a definite syndrome. This came to be called the Morgagni, or Morgagni-Stewart-Morel, syndrome.

Hyperostosis, discovered at necropsy or radiologically, is not very uncommon in psychiatric conditions, and this may have tempted many authors to assume a causal relationship, for in many papers there is no clear definition of the syndrome and the bony changes are loosely spoken of as if they constituted the syndrome itself. Grollman and Rousseau (1944) have even stated that the diagnosis could be made without *x*-ray confirmation of bony change. Sherwood Moore (1936b) found hyperostosis frontalis interna in 1·44% of 6,650 skulls examined radiologically, and calvarial hyperostosis of all sorts in a total of 3·48%, from which he defined a symptom complex which he referred to as " metabolic craniopathy ".

Medical literature is replete with accounts of the condition, e.g., van Bogaert (1930), Fracassi and Marelli (1936), Roger (1938), Notkin (1953). Grollman and Rousseau (1944) found calvarial hyperostosis in 78 or 4·1% of 1,620 skulls of mental patients in North Carolina. No authors have so far described a consistent or specific neuropsychiatric picture which they found associated with hyperostosis frontalis interna in a significant number of cases. Isolated cases have been described in which cerebral atrophy has been demonstrated by pneumo-encephalography (Moore, 1944), and some authors have suggested, without very much evidence, that hyperostosis damaged the brain directly. This may occur in very rare cases. Roth (1941), who discusses this question, believes that the cranial bone changes and the psychiatric disturbances are of separate origin.

Some authors (Mortimer, 1938, and André Calamé, 1951) believe in an endocrinopathic aetiology. Calamé refers to 60 personally observed cases and considers that the syndrome is a real entity and due to a lesion of the adrenal cortex involving pituitary relationships and associated with increased intracranial tension.

Since hyperostosis frontalis interna has been looked for and demonstrated chiefly in mental patients, some case can be made for associating it with neuropsychiatric disturbances, and the literature as a whole inclines to a belief in a syndrome called variously hyperostosis frontalis interna, the Stewart-Morel syndrome, l'hyperostose frontale interne, metabolic craniopathy, or Morgagni's syndrome. There is, however, some difference of opinion as to whether any association of skull change with neuropsychiatric, metabolic, or endocrine disturbances is fortuitous. It also seems well established that similar bony changes can be found in association with other conditions, such as dystrophia, myotonica, certain tumours of the brain and its coverings, and even after encephalitis in childhood (Wakeley and Orley, 1938).

Pedersen (1947) estimated that hyperostosis occurs in the skulls of 5% of normal people before 40 and 12% after 40 ; and other workers (e.g., Schneeberg, Woolhandler, and Levine, 1947) regard cranial hyperostosis as a not uncommon incidental skull abnormality in women, coincidental with various clinical conditions.

From examination of a considerable and varied psychiatric case material, we have been unable to suspect the existence of this syndrome or hyperostosis frontalis interna without radiological evidence, and we have not been satisfied that we could associate the radiological evidence with psychiatric or endocrine symptoms with sufficient confidence to make a diagnosis of the syndrome. We have observed that prognosis did not seem to be affected by hyperostosis frontalis interna and the clinical outcome in our cases was in accordance with the psychiatric diagnosis, irrespective of skull change.

We have followed up a case previously referred to by Hemphill and Stengel (1940) which is relevant to the question. These authors investigated a

familial craniopathy and described post-mortem findings in the mother of the patient. At that time the patient showed a paranoid psychiatric picture. She was thick-set, obese, with some degree of hirsutism. Her physical constitution resembled that of her father. After the publication of the paper, the patient, who had been married, was divorced and re-married. Hyperostosis frontalis interna was demonstrated by radiography in her first child, who appears to have had a normal development and schooling, and is now believed to be normal, aged about 15, but she has not been available for examination since the divorce. There are four normal children as a result of the re-marriage, in whom radiological examination shows normal skulls. The patient is supervised by her husband ; she has an extensive system of paranoid delusions with thought disorder, and manages her home very badly. There is now (15 years after the condition was diagnosed) no evidence of endocrine disturbance (other than what appears to be a constitutional or familial obesity) ; no evidence of an organic dementing process suggesting interference with brain ; no hypertension ; and no neurological disorder. In this case, the fairly confident diagnosis of Morgagni's syndrome that was made in 1940 could not now be accepted, according to the definition of the syndrome then agreed on, and the case must now be regarded as chronic paranoid schizophrenia, with a fortuitously associated, non-progressive familial craniopathy.

There is clearly, therefore, a fundamental divergence of opinion on this matter, and with this in mind we attempted the present study, in order to clarify this problem, if possible, by clinical and laboratory means.

We here present 11 female psychiatric cases in which a variety of biochemical, endocrine, and neuropsychiatric investigations were made.

Methodology

Eleven female cases were studied. Four of these were discovered by the routine skull radiography of 120 chronic mental patients, the remainder (seven) during the investigation of acute psychiatric admissions. Five major investigations were made : neuropsychiatric, electroencephalographic, endocrine, metabolic, and a miscellaneous group.

The miscellaneous group of investigations consisted of blood pressure, blood count, blood Wassermann reaction and analysis of C.S.F., and the results were all within normal limits ; the maximum and minimum blood pressures were 150/85 mm. Hg (Case 3) and 105/70 mm. Hg (Case 9). Hypertension has been described in many reports. Grollman and Rousseau (1944) found it in 16 out of 40 patients, and Roth (1941) in five out of eight. It was not, however, present in our series.

The results of the other investigations are shown in the Tables.

Results

Neurological abnormalities were present in Case 1 only (presenile dementia). The remainder were normal and none of the findings of Moore (1935) (cranial nerve defects, aphasia or apraxia, ataxia, narcolepsy, etc.) were present. Psychiatrically there was no specific diagnostic picture and no evidence of the intellectual slowness with depression and anxiety, or disturbances of temperament and character, which could be associated with hyperostosis, as emphasized by Schiff and Trelles (1931). The electroencephalographic results were in agreement with the clinical diagnosis. The literature reports few air-encephalographic investigations ; in six out of our 11 patients, air-encephalography was performed, and of these only one (the case of presenile dementia) showed the anticipated atrophy of the frontal and temporal regions.

No anomaly was noted in either the present state of menstruation or the time of menopausal cessation.

TABLE I

NEUROPSYCHIATRIC, ELECTROENCEPHALOGRAPHIC, AND AIR-ENCEPHALOGRAPHIC FINDINGS

No.	Age	Neurological State	Psychiatric State	Electroencephalogram	Air-Encephalogram
1	42	Transitory phases of apraxia, aphasia, and dyslexia. Nil else	Dementia, probably presenile	Abnormal, typical of diffuse organic change	Cortical atrophy frontal and left temporal lobes
2	42	Normal	Depressive stupor	Non-specific dysrhythmia	Normal
3	53	,,	Neurotic depression, epilepsy	Diagnostic of epilepsy	Not done
4	26	,,	Reactive depression, intellectually subnormal, epilepsy	,, ,, ,,	Normal
5	59	,,	Neurotic depression	Some immature and epileptiform features	Not done
6	38	,,	Chronic paranoid schizophrenia	Normal	Normal
7	42	,,	,, ,, ,,	,,	,,
8	77	,,	Chronic depression, intellect normal	,,	Not done
9	73	,,	Chronic depression, intellect normal	Dysrhythmia, with some lowering of convulsive threshold	Normal
10	74	,,	Senile depression, minimal intellectual failure	Non-specific dysrhythmia. Just outside normal limits	Not done
11	66	,,	Recurrent agitated depression, intellect normal	Normal	Normal

TABLE II
ENDOCRINE FINDINGS

No.	Age	Menses	Secondary Sex Characteristics	*Ketosteroids (total/24 hours)	†Adrenal Response	‡Thyroid Activity
1	42	Regular	Normal	9·4	Positive	Normal
2	42	Ceased 2½ years ago	Slight moustache. Diamond formation pubic region	13·6	Positive	Normal
3	53	Ceased 2 years ago	Normal	16·4	Positive	Normal
4	26	Regular	Normal	15·0	Positive	Normal
5	59	Ceased 3 years ago	Normal	14·6	Positive	Normal
6	38	Regular	Slight moustache	9·0	Positive	Normal
7	42	Regular	Normal	8·6	Positive	Normal
8	77	Ceased many years ago	Normal	2·9	Positive	Normal
9	73	Ceased many years ago	Much facial hair	5·4	Positive	Normal
10	74	Ceased many years ago	Normal	8·4	Positive	Normal
11	66	Ceased 16 years ago	Normal	8·6	Positive	Normal

* Ketosteroids : Normal values, age 16 to 40, 5·1 to 19·6 mg./24 hours urine (Dorfman, 1948).
† Adrenal response : This is indicated by a drop in eosinophils of 30%, and increases in uric-acid/creatinine ratio of 20% and in ketosteroid/creatinine ratio of 5% (Reiss, Hemphill, Early, Maggs, Cook, and Pelly, 1951).
‡ Thyroid activity was measured by radio-iodine (Haigh, Reiss, and Reiss, 1954).

TABLE III
METABOLIC FUNCTIONS

No.	Age	Obesity	*Plasma Cholesterol (mg.)	†Serum Calcium (mg.)	‡Serum Phosphate (mg.)	§Alkaline Phosphatase	Glucose Tolerance Test
1	42	Nil	216	9·6	4·0	5·95	Normal
2	42	Nil	212	9·5	4·2	5	Normal
3	53	Nil	180	10·4	5·1	6·4	Normal
4	26	Nil	210	10·4	4·5	6	Normal
5	59	Slight abdominal	224	9·46	4·8	4·2	Normal
6	38	Nil	190	9·2	4·4	6	Normal
7	42	Nil	132	9·6	3·1	4·1	Normal
8	77	Slight abdominal	170	9·8	3·6	5·4	Normal
9	73	Nil	220	10·6	4·0	9·95	Normal
10	74	Nil	179	10·5	3·5	6	Normal
11	66	Nil	200	10·8	4·1	7·4	Mildly diabetic

Normal values : * Plasma cholesterol, 140 to 215 mg./100 ml.
† Serum calcium, 9·6 to 10·9 mg./100 ml.
‡ Serum phosphate, 2 to 5 mg./100 ml.
§ Alkaline phosphatase, 5 to 10 units/100 ml.
(King, 1951)

Three of the 11 patients showed slight masculine distribution of hair—facial, chest, pubic. None of these, however, demonstrated any other associated endocrine dysfunction. Grollman and Rousseau (1944) observed that the principal endocrine disturbances in their cases were amenorrhoea and hirsutism, and in two of the current group under review (aged 42 and 38) the amenorrhoea and hirsutism might possibly be important, but more likely are related to an early menopause. The low ketosteroid value (2·9 mg.) in Case 8 is attributable to old age (77).

These findings are substantially within normal limits. The results of metabolic investigation have hitherto varied. Grollman and Rousseau (1944) considered the principal metabolic anomaly to be obesity of the rhizomelic type, but in this group only two patients showed obesity to a slight degree. Roth (1941), on the other hand, found that six out of eight patients showed obesity, and, unlike Grollman and Rousseau's patients, all his eight cases gave a diabetic type of curve on glucose tolerance test ; also two of Roth's patients gave increased values for serum calcium. In the present group only one gave an abnormal sugar tolerance curve. None gave calcium values outside normal. In the case of the patient with the abnormal curve, no glycosuria was found to be present and the high renal threshold might well represent a state of affairs not uncommon in the old.

Discussion

In view of the essentially normal or negative findings and the varying psychiatric pictures it seems impossible to be able to identify a definite syndrome. It is felt that the above results show that thickening of the internal table of the frontal bone in psychiatric cases does not imply any regular association of pathological deviations in endocrine, metabolic, biochemical or neurological fields. They agree with the view of Schneeberg and his colleagues (1947) that hyperostosis is incidental and may on occasion be associated with other signs and symptoms so as to produce an apparent Morgagni's syndrome, but that it may occur independently or in combination with other skull anomalies in association with conditions such as dystonia myotrophica (Caughey, 1952).

The statement of Grollman and Rousseau (1944) that although " *x*-ray changes need not be present . . . they remain the most constant and reliable characteristic of the disorder " must be qualified, in spite of the large number of cases they have investigated. Clinical and laboratory investigations in our series have shown that a definite condition of hyperostosis need *not* be associated with a definite syndrome and the occurrence of the bony changes may be entirely coincidental.

Summary

Eleven female patients suffering from various psychiatric disorders with associated hyperostosis frontalis interna were investigated. Ketosteroids, adrenal response activity, thyroid activity, physical development, and endocrine state were within

normal limits. There was no hypertension and no obesity. Electroencephalographic and neurological tests, when abnormal, were in keeping with the psychiatric diagnosis.

No relationship of symptomatology was found to suggest a diagnosis of Morgagni's syndrome.

It is concluded that hyperostosis frontalis interna may occur fortuitously with psychiatric or endocrine disorders, but it seems probable that Morgagni's syndrome—if it exists as a psychiatric identity—is very much rarer than hyperostosis frontalis interna in psychiatric patients.

BIBLIOGRAPHY

Bogaert, L. van (1930). *J. Neurol. (Brux.)*, **30**, 509.

Calamé, A. (1951). *Le Syndrome de Morgagni-Morel.* Masson, Paris.

Caughey, J. E. (1952). *Brit. med. J.*, **1**, 137.

Delmas-Marsalet, M. P. (1938). *J. Med. Bordeaux*, **115** (2) 661.

Dorfman, R. I. (1948). In *The Hormones*, ed. Pincus, G., and Thimann, K. V., Vol. 1, p. 467. Academic Press, New York.

Fracassi, T., and Marelli, F. L. (1936). *Rev. argent. Neurol. Psiquiat.*, 2, 65.

Greig, D. M. (1928a). *Edinb. med. J.*, **35**, 165.

——(1928b). *Ibid.*, **35**, 237.

Grollman, A., and Rousseau, J. P. (1944). *J. Amer. med. Ass.*, **126**, 213.

Haigh, C. P., Reiss, M., and Reiss, J. M. (1954). *J. Endocr.*, **10**, 273.

Hemphill, R. E., and Stengel, E. (1940). *J. ment. Sci.*, **86**, 341.

Henchen, F. (1936). *Acta path. microbiol. scand.*, Suppl. 26, 98.

King, E. J. (1951). *Micro-analysis in Medical Biochemistry*, 2nd ed. Churchill, London.

Knies, P. T., and Le Fever, H. E. (1941). *Ann. intern. Med.*, **14**, 1858.

Moore, M. T. (1944). *Arch. intern. Med.*, **73**, 7.

Moore, S. (1935). *Surg. Gynec. Obstet.*, **61**, 345.

——(1936a). *Arch. Neurol. Psychiat. (Chicago)*, **35**, 975.

——(1936b). *Amer. J. Roentgenol.*, **35**, 30.

Morel, F. (1930). *Hyperostose frontale interne. Syndrome de l'hyperostose frontale interne avec adipose et troubles cérébraux.* Doin, Paris.

Morgagni, J. B. (1765). *De sedibus, et causis morborum per anatomen indagatis*, 2nd ed., book 2, epis. 27. Sumptibus Remondinianis, Patavii.

Mortimer, H. (1938). *Res. Publ. Ass. nerv. ment. Dis.*, 1936, **17**, 222.

Notkin, J. (1953). *Amer. J. Psychiat.*, **109**, 929.

Pedersen, J. (1947). *Acta med. scand.*, **128**, 71.

Reiss, M., Hemphill, R. E., Early, D. F., Maggs, R., Cook, E. R., and Pelly, J. E. (1951). *J. clin. exp. Psychopath.*, **12**, 171.

Roger, A. A. (1938). *Canad. med. Ass. J.*, **38**, 129.

Roth, N. (1941). *Amer. J. Psychiat.*, **98**, 63.

Schiff, P., and Trelles, J. O. (1931). *Encéphale*, **26**, 768.

Schneeberg, N. G., Woolhandler, G., and Levine, R. (1947). *J. clin. Endocr.*, **7**, 624.

Schneider, E. (1936). *Med. Klin.*, **32**, 487.

Stewart, R. M. (1928). *J. Neurol. Psychopath.*, **8**, 321.

Wakeley, C. P. G., and Orley, A. (1938). *A Textbook of Neuroradiology.* Baillière, Tindall and Cox, London.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 46.

A FAMILY WITH THE PROGRESSIVE HYPERTROPHIC POLYNEURITIS OF DEJERINE AND SOTTAS

BY

P. D. BEDFORD and F. E. JAMES

From Cowley Road Hospital, Oxford, and Chipping Norton, Oxon

Progressive hypertrophic polyneuritis (Dejerine and Sottas, 1893) is a well established clinico-pathological entity which is mentioned in most standard medical textbooks. It is, however, a very rare disease. Since the paper by Russell and Garland (1930) the only cases recorded in British medical journals have been an Australian family (Cooper, 1936). Since Sloane (1939) comprehensively reviewed the literature, communications have appeared sporadically in the world's medical press at the rate of approximately one every three years.

De Bruyn and Stern (1929) have criticized each of the adjectives "progressive", "familial", "hypertrophic", etc., which have in varying combinations been applied to describe the syndrome of Dejerine and Sottas; the nature of the polyneuritis has frequently been atypical and has often not conformed with one or more of these descriptions. This communication, however, describes a family in the United Kingdom affected with the disease in its typical form.

The genealogical tree is shown in the Figure. So far as can be ascertained there have been no consanguineous marriages in this family. All its available members have been personally examined. Details have been sought, and information cross-checked concerning all those who have died or for other reasons are not available for examination. The results are also shown in the Figure.

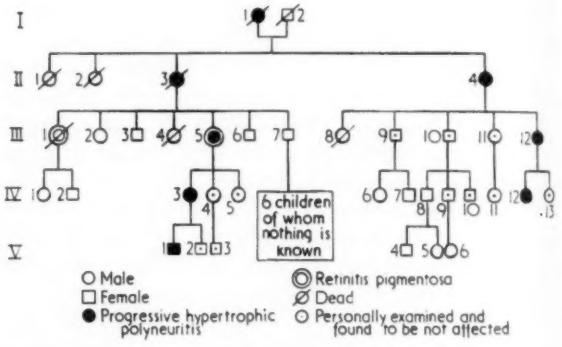
Eight cases of progressive hypertrophic polyneuritis have come to light. The two patients who died long before this enquiry began were probably mildly affected. The case histories of the other six are presented in this paper; two are affected severely, two mildly, and two minimally.

Another hereditary disease—retinitis pigmentosa—also occurs in this family but in only two siblings.

Case Reports

Case 1 (C.R.H. No. 2459).—Benjamin B. (**II.4** in Fig.), a male aged 80, is an intelligent person who gives a good account of himself. He was perfectly well until the age of 25 when he noticed that his legs occasionally "let me down". This was the first indication of the weakness of the legs which since then has been very slowly progressive. At about the same time he began to notice occasional tinglings, numbness, and "pins and needles" in the hands and feet. These paraesthesiae have persisted since then and have always been more obtrusive in the feet than in the hands.

FIGURE



I.1 is stated by **II.4** to have had the disease.
I.2 died aged 50–60; she was not affected.
II.1 was killed in an accident when a youth.
II.2 died young and nothing is known about him.
II.3 is stated by **II.4** and **III.10** to have had the disease.
II.4 is Case 1.
III.1 Very probably had retinitis pigmentosa; he was killed in World War 1 aged 25–30.
III.2 and **III.3**—nothing is known of these sibs.
III.4 died in infancy aged 6 months.
III.5 is Case 2 and has retinitis pigmentosa.
III.6 and **III.7**—nothing is known of these sibs. except that **III.7** had six children.
III.8 was killed in World War 1 aged about 40; nothing else is known about him.
III.9, III.10, and **III.11** are aged 56, 51, and 47 respectively.
III.12 is Case 5.
IV.1 and **IV.2**—nothing is known of these sibs.
IV.3 is Case 3.
IV.4 and **IV.5** are aged 29 and 30 respectively.
IV.6 and **IV.7**—nothing is known of these sibs.
IV.8 is aged 28 but nothing else is known of her.
IV.9, IV.10, IV.11, and **IV.13** are aged 24, 17, 8, and 11 respectively.
IV.12 is Case 6.
V.1 is Case 4.
V.2 and **V.3** are aged 1 and 9 respectively.
V.4, V.5, and **V.6** are aged 5, 4, and 4 respectively; nothing else is known of them.

Some years later there gradually developed an unsteadiness of gait. This ataxia is conspicuous only in the dark or when the eyes are closed ; it has never been severe, but is now worse than formerly. There has been no disturbance of sphincter control and no ocular abnormality but his neurological condition has been steadily though extremely slowly progressive. He was in the Royal Air Force in the First World War in Category C3 (he does not know why but " probably because of my feet ").

His account of the family history is as follows—and differs from that given by his nephew (**III.5**, Case 2). (When challenged with this discrepancy the patient retorted that his nephew " doesn't know what he's talking about " !)

The patient states that his father " used to have difficulty in getting about because of his feet " and that his hands were " all doubled up " but that " this didn't bother him ". When asked whether the deformity of his father's hands and feet was like his own he answers " Yes—but nothing like so bad ". His mother was unaffected : he does not know of what she died but she lived to " between 50 and 60 ". So far as is known the founders of the family were not consanguineous ; they both however derived from Over Norton, a tiny hamlet near Chipping Norton in Oxfordshire, and the possibility of inbreeding cannot be excluded. His brother (**II.3**) died " over 80 " and " had feet and hands a bit like mine but nothing like so bad ; they didn't bother him—he got used to it ". His brother's wife was unaffected ; she " died young—about 50 ". As far as he is aware, all his children and grandchildren are normal, but he believes that his nephew (**III.5**) has feet and hands " a bit like mine—but not so bad ". His account is corroborated by **III.10** (his daughter—an unaffected female) who states that " Uncle Jim, i.e., **II.3**, used to walk like father and throw his feet about ".

On examination the cranial nerves reveal no abnormality and, in particular, the pupils and ocular fundi are normal and there is no nystagmus.

There is symmetrical weakness and wasting of distal distribution in the arms and legs, the legs being more severely affected than the arms. The hands are more affected than the forearms, and the upper arms and shoulders not at all. There is bilateral flaccid foot drop with conspicuous wasting of the muscles below the knee and only slight weakness and wasting of both quadriceps femoris. The muscles of the hips and trunk are normal.

There is slight impairment of sensibility to pin-prick in the fingers of both hands and considerable impairment in both legs below the knee. (The proximal limit of hypo-algesia is ill-defined in both arms and legs.) Touch, deep pain, and temperature sensations are reasonably well perceived. Vibration perception is impaired in both hands and absent in both legs below the knee. Postural sensibility is normal in the hands but is grossly impaired in the toes, ankles, and knees.

There is complete tendon areflexia except for a sluggish jaw jerk and a barely perceptible right triceps jerk. The cutaneous reflexes are preserved ; the plantar responses are flexor. Romberg's sign is positive.

His gait is high stepping and rather wide based ; it becomes grossly ataxic when the eyes are closed. There is incoordination of " sensory type " in that the finger-nose and heel-knee tests are poorly and inaccurately performed with the eyes closed, but are accurately carried out under visual control. There is no evidence of cerebellar disturbance. The external popliteal nerves, as they wind round the fibulae, and the ulnar nerves at the elbow are grossly hypertrophied. The calves are not tender. There is a single telangiectasis of the forehead but no abnormality of any other system. The cerebrospinal fluid is normal and the Wassermann and Kahn reactions negative.

A biopsy specimen of the cutaneous division of the musculo-cutaneous nerve of the left foot is reported on as follows (S.H. No. 1334) :—

> " A length of peripheral nerve 2 cm. long by 3 mm. wide by 1 mm. thick. It is made up of several well separated bundles. No nodularity is visible macroscopically. Histology shows the characteristic onion formation of hypertrophic neuritis. There is some degeneration with an increase in the number of Schwann nuclei and also some increase in the collagen around the fibres."

This is a severe symmetrical polyneuropathy of distal distribution affecting motor function more than sensory and the legs more than the arms. The condition has been very slowly progressive. The peripheral nerves are grossly hypertrophied. Biopsy confirms the diagnosis of progressive hypertrophic polyneuritis.

Case 2.—Albert B. (**III.5** in Fig.), a male aged 58, is the nephew of Case 1.

His infancy was normal except that he walked rather late. In childhood he noticed that he stumbled at games because " my feet dropped ". He was never as nimble, fast, or agile as other children. In adolescence he began suffering from " pins and needles ", numbness and tingling in the legs, which symptoms have continued ever since but are less obtrusive now than formerly. There have been no paraesthesiae in the arms. At the same time, and of gradual onset, he noticed himself to be unsteady on his feet. This ataxia is of " sensory " type in that he is perfectly well able to preserve his balance during the day or when his eyes are open, but cannot do so in the dark or with his eyes closed. Weakness of both legs together with bilateral foot drop developed very gradually over the years but became much worse at about the age of 40 to 50 following a period of immobilization for a Pott's fracture of the left ankle. His disability has been steadily but very slowly progressive and is even now not severe. There has been no disturbance of sphincter control. He joined the Army in the First World War in medical category A1 but was demobilized in Category B2 because of a non-penetrating shrapnel wound in the posterior part of the head. He first noticed a defect in night vision some years ago and this has become slowly but steadily worse. At the same time he noticed difficulty in rapid visual accommodation for near objects. This is due to a congenital pigmentary defect of the retina (retinitis

pigmentosa) for which he has attended the Oxford Eye Hospital.

His account of the family history differs from that given by his uncle (**II.4,** Case 1) and his cousin (**III.10**). He does not remember his grandfather very well but he believes that he had nothing wrong with his hands or feet; he cannot remember his grandmother. He states that his father "had abnormal thumbs" but walked well, could pick up nails to mend his own boots, and could climb ladders to clean lamps until he was 74 years of age: he died aged 84. His mother died of heart failure when aged 50. His eldest brother, who was killed in the First World War, "had eyes just like mine; he couldn't see in the dark either", but other than this visual defect "he was perfectly sound". Initially he stated confidently that except for his uncle no one else in the family was affected. At a later date, however, when confronted with other affected members of the family, he agrees that his account is incomplete and probably erroneous, and offers the shrewd observation that "you can see it in the thumbs first".

On examination he strongly resembles his uncle. He is a heavily built, powerful, intelligent man of somewhat euphoric disposition. He has a single telangiectasis on the forehead and the scar of an old shrapnel wound posterior to the inion. There is no abnormality of any system other than the neurological.

His night vision is poor but in full light his vision is excellent except for near objects. There is a fully correctible myopia of about three dioptres for which he wears "reading glasses". There is slow, defective, and incomplete ocular accommodation for near objects. The ocular fundi show the classical pigmentary changes of retinitis pigmentosa; there is no optic atrophy. Otherwise the cranial nerves are normal; the pupils react normally to light and there is no nystagmus.

There is wasting of the thenar eminences of both hands and wasting of the legs below the knees with bilateral flaccid foot drop. There is moderate diffuse weakness of the muscles of the hands and forearms and considerable weakness of the legs and feet below the knees. The power of the rest of the musculature is excellent.

The painful quality of pin-prick is not perceived over both hands and the medial borders of both forearms, and over the feet and medial aspects of both legs below the knees; the upper limits of this hypo-algesia are not clearly defined. Light touch is impaired over the same areas but temperature sensibility is preserved. Vibration is less well perceived in the hands than proximally and is absent in both legs below the knees. Postural sensibility is normal in the arms but is impaired in the legs; he is unable to point accurately to his great toes with his eyes closed.

There is complete areflexia of the tendon jerks.

The cutaneous reflexes are preserved and the plantar responses flexor. Coordination is impaired in the arms and legs, judged by the finger-nose and heel-knee tests, only when his eyes are closed; the tests are accurately performed with the eyes open.

Romberg's sign is positive.

There is no evidence of cerebellar disturbance.

His gait is wide based and high stepping and is grossly ataxic with his eyes closed.

The ulnar nerves and to a greater degree the external popliteal nerves as they wind round the neck of the fibulae are grossly enlarged.

This is a severe mixed sensory and motor polyneuropathy of very gradual progression associated with conspicuous hypertrophy of the peripheral nerves.

The patient also has retinitis pigmentosa.

Case 3.—Ronald Albert B. (**IV.3** in Fig.), a male aged 34, is the son of Case 2.

This patient was born with "funny feet". He has never been able to run properly and this disability is most marked when he tries to run fast. His hands have "always been clumsy" but "are no worse now than they always were". This clumsiness applies only "with little things like a pin; I don't usually get it first time". He also has some difficulty with small buttons, e.g., those on a shirt. He feels that his symptoms are trivial and have been quite stationary throughout his life. He denies paraesthesiae. He is not unsteady in the dark. His vision is excellent both by night and by day; his colour vision is normal. He plays games but "I am a little clumsy on my feet" (he has someone to run for him when batting at cricket but "manages fairly well" when he fields in the slips). He served for six years in the late war in an anti-aircraft battery in the Army, in medical Category B7 because of his feet. He does a full day's work as a heavy manual labourer, using his arms and shoulders rather than his feet. His work is so heavy that he occasionally suffers salt depletion cramps. He is inordinately proud of his physical prowess and appears to have somewhat over-compensated for the disability of his feet.

On examination he is a slightly built, intelligent man who conceals an anxiety about his physical condition under an aggressive euphoria. There is a single "spider angioma" on the right cheek but no abnormality elsewhere than in the nervous system. The cranial nerves are normal; in particular the ocular fundi and pupils are normal and there is no nystagmus. There is diffuse wasting of the small muscles of both hands (more conspicuous in the right than the left), and the opponens pollicis muscles are particularly affected. The palmar surfaces of the hands are flattened and the dorsal aspects show marked hollowing between the extensor tendons. His feet are clawed with callosities on both soles, and there is bilateral flaccid foot drop—again more marked on the right than the left. The small muscles of both feet and of the anterior tibial group of muscles in both legs are wasted. There is slight weakness of extension and even less of flexion of the hands, wrists, and fingers, and moderate weakness of dorsiflexion of both feet. Otherwise power is excellent throughout.

The painful quality of pin-prick is poorly perceived over the distal phalanges of the hands and in both legs below the knees—particularly in the feet. Touch and temperature sensibilities appear to be unimpaired.

Postural sensibility is normal in the arms but is defective in the legs; he fails to point accurately to his great toes with his eyes closed. Vibration perception is impaired in both feet. There is complete areflexia of the tendon jerks but the cutaneous reflexes are preserved. The plantar reflexes are flexor.

When the eyes are closed coordination is impaired (finger-nose test; heel-knee test), but the tests are accurately performed with the eyes open.

His gait shows the high stepping quality of mild flaccid foot drop and is ataxic when the eyes are closed but not when they are open.

Romberg's sign is not present.

There is no evidence of cerebellar disturbance.

The ulnar nerves at the elbow and the external popliteal nerves as they wind round the fibulae are grossly hypertrophied (the right ulnar nerve is approximately $\frac{3}{8}$ in. (nearly 1 cm.) in diameter).

This is a mild mixed sensory and motor polyneuropathy present since childhood and showing little or no progression. It is associated with gross hypertrophy of the peripheral nerves.

Case 4.—Barbara B. (**V.1** in Fig.), a female aged 10, is the daughter of Case 3.

Her mother states that she " has feet like her father's " and that she is unable to run as fast as other children; this was first noticed when she began to walk—which she did rather late—at the age of 5. She is otherwise perfectly well.

On examination she is a pleasant, well built, intelligent child. She is left handed. The only abnormalities detected are slight weakness of dorsiflexion of both feet; complete areflexia of the tendon jerks with preservation of the cutaneous reflexes; slight ataxia when walking with the eyes closed, with a slight tendency to flaccid foot drop; some impairment of vibration perception in the feet; slight impairment of large joint postural sensibility (as manifested by failure to point accurately to the great toes with the eyes closed); slight " sensory " ataxia as shown by the heel-knee test with the eyes closed; and conspicuous enlargement of the left external popliteal nerve at the neck of the fibula.

There are no other symptoms; there are no paraesthesiae. No other abnormality can be detected and in particular there is no obvious muscle wasting. The pupils and ocular fundi are normal and there is no nystagmus.

This is a minimally affected case of progressive hypertrophic polyneuritis, but whether or not it will subsequently progress is uncertain.

Case 5.—Dennis B. (**III.12** in Fig.), a male aged 40, is the son of Case 1.

He is an engineer's labourer who is aggressively confident that " there's nothing wrong with me ". His feet have been " slightly deformed " for as long as he can remember but have given him no trouble whatever. His infancy and childhood were uneventful. His athletic ability at school was average. He joined the Army in the late war in medical Category A1 but was regraded B7 because of his feet.

On direct questioning he admits to paraesthesiae in the left leg and both hands " for some years ". This is his only symptom; it comprises tingling, " pins and needles ", and numbness unrelated to posture, sleep, or activity. The paraesthesiae have always been mild but are slightly more obtrusive now than formerly. He is otherwise perfectly well.

On examination he is of small stature (64 in.) but is well proportioned. He bears a strong facial resemblance to his father. There is no abnormality in any system other than the neurological.

The cranial nerves are normal as in particular are the ocular fundi and pupils, and there is no nystagmus. There is flattening of the thenar eminences of both hands with conspicuous weakness and wasting of the opponens pollicis and flexor brevis pollicis of both hands. There is moderate diffuse weakness of both flexion and extension of the fingers of both hands (and more especially of flexion), but no muscular wasting in the upper limbs can be detected elsewhere. There is bilateral pes cavus with slight flaccid weakness, and wasting of the dorsiflexors of both feet. There is slight sensory impairment in the hands in that pain (pin-prick) and light touch are poorly perceived in the first and second fingers of both hands. Vibration perception and postural sensibility are slightly impaired in the legs below the knees, but not elsewhere, and all other sensory modalities appear to be normal.

All the tendon reflexes are extremely sluggish even on reinforcement. The cutaneous reflexes are preserved and the plantar responses flexor. Coordination is normal in the arms but is slightly impaired in both legs. This mild ataxia is of " sensory " type in that the tests are accurately performed with the eyes open but not with the eyes closed.

Romberg's sign is not present.

There is a suggestion of foot drop on walking, but otherwise the gait is normal. The right external popliteal nerve, as it winds round the neck of the fibula, and the cutaneous division of the left musculo-cutaneous nerve of the foot are grossly enlarged; the other peripheral nerves appear to be normal.

This is a long-standing, mild, mixed polyneuropathy affecting the hands and feet, associated with conspicuous hypertrophy of two peripheral nerves.

Case 6.—Robert B. (**IV.12** in Fig.), a male aged 14, is the son of Case 5.

This boy admits to no symptoms. He is a member of the school association football team and passed his infant " milestones " without incident and at the normal age.

On examination he is an intelligent, alert youth of good physique. The only abnormalities detected are slight flattening of the thenar eminences with weakness and wasting of the muscles of both thumbs (especially of the flexor brevis and the opponens pollicis), moderate enlargement of both median nerves at the wrist, and impairment of vibration perception in the feet. All the tendon reflexes are sluggish, even on reinforcement. The cutaneous reflexes are normal and the plantar

responses flexor. The other peripheral nerves do not appear to be enlarged ; the ocular fundi and pupils are normal and there is no nystagmus. His feet are normal and there is no foot drop.

This is a minimally affected case of progressive hypertrophic polyneuritis, but whether or not it will subsequently progress is uncertain.

In none of the cases was fasciculation of muscles visible. There were no neurofibromata, no abnormal cutaneous pigmentation, and no spinal deformity.

Discussion

There are many inconstant features of the syndrome of Dejerine and Sottas as is indicated by the many adjectives used to describe the polyneuritis. The only constant clinical feature is muscular weakness and wasting which may be slight, moderate, or severe. Sensory symptoms and signs are usually present but rarely obtrusive and frequently absent. Thickening and enlargement of one or several of the peripheral nerves frequently occurs and may be extreme. When present this feature is virtually pathognomonic and clearly distinguishes the syndrome from Tooth's (1886) " peroneal muscular atrophy ". But enlargement of the peripheral nerves may not be clinically apparent if of minor degree, and indeed may not occur at all. The histological picture, however, is characteristic and pathognomonic although biopsy may be inconclusive as not all the nerves may be affected at any one time nor to the same extent. De Bruyn and Stern (1929) criticize the term " interstitial neuritis " since the lesion is essentially a hypertrophy of the sheath of Schwann. For this reason Bielschowsky (1922) considers that the disease is related to neurofibromatosis. The adjective " progressive " as applied to the disorder is also open to criticism, for although there is usually a gradual and very slow deterioration, the progress of the disease may halt spontaneously at any stage, and may thereafter show no advance whatever.

Although usually a heredo-familial disorder, many of the recorded cases have occurred sporadically and in isolation in fully documented and otherwise unblemished family trees. Thus the adjective " familial " is also open to criticism. From a study of the published families the mode of inheritance would appear to be variable. Snyder (1941) states that it is usually a recessive characteristic ; and in view of the many isolated cases published this may well be so. In many families, however, the mode of inheritance would appear to be dominant if the definition be accepted that a characteristic is dominant if it affects parent and child or several sibships in the same generation.

In the family described here the disease appears to be inherited as a heterozygous dominant characteristic if the statements of **II.4** (Case 1) and **III.10** be accepted as true. The initial discordant account of the family history given by **III.5** (Case 2) introduces the possible anomaly of **II.3** being unaffected. The subsequent purity of heterozygous dominance in the line of **II.3** would be difficult to explain except on the basis of an adulterous relationship between his wife and an affected male, e.g., **II.4** (Case 1) which is of course a reasonable alternative hypothesis. Further information regarding this possibility may become available from a study of the blood groups of the members of the family which is at present being carried out. It is, however, highly probable that **II.3** was in fact affected, for both **II.4** and **III.10** have independently asserted this, while **III.5** originally denied it but subsequently retracted his denial. The chances of any child being affected in this family are difficult to forecast accurately. Although no child can have the disease unless the father or the mother is affected, the likelihood of its reappearance in the lines of **IV.3** and **III.12** seems considerable.

It is of interest to note that after the discovery of Cases 1 and 2 (**II.4** and **III.5**) the initial enquiry and admittedly superficial examination of the other members of the family conducted by one of the authors failed to disclose the remaining cases. This led to the erroneous genetic explanation of the occurrence by spontaneous mutation of a recessive gene of low penetrance. Only after very careful further enquiry and examination did the true facts come to light and the heterozygous dominant transmission be revealed. By analogy, it is possible that some of the sporadic and isolated cases which have been published and for which a recessive mode of inheritance has been postulated (Snyder, 1941) were the result of the same error. It cannot be too strongly emphasized that in an investigation of a heredofamilial disorder the histories must be cross-checked at every possible point and that careful personal examination of all the available members, whether alleged to be unaffected or not, is an essential requisite.

Several cases of the syndrome of Dejerine and Sottas have been described in which pupillary anomalies have been noted, such as anisocoria, and very slow reaction to light and convergence (François and Descamps, 1949). At one time the Argyll-Robertson pupil was erroneously thought to be an integral part of the disorder (De Bruyn and Stern, 1929). No case however has previously been reported with retinitis pigmentosa as had Case 2 (**III.5**) whose eldest brother (**III.1**) very probably

was similarly affected. Retinitis pigmentosa is carried by a recessive gene, and the association in this family of the two hereditary conditions—the heterozygous dominant polyneuritis and the recessive retinitis—is probably fortuitous.

Summary

A family of five generations is described in which progressive hypertrophic polyneuritis (syndrome of Dejerine and Sottas) is inherited as a heterozygous dominant characteristic.

Eight members of the family were affected, two severely, four mildly, and two young children minimally. Case histories are presented of the six who were available for examination. Histological confirmation of the diagnosis was sought and obtained in one case.

One affected male also has retinitis pigmentosa and it is highly probable that an otherwise healthy brother had the same inherited retinal disorder.

We are grateful to Dr. P. M. Daniel for the pathological report, to Dr. W. Ritchie Russell for his helpful criticism, and to Dr. F. Whitehead and Mr. E. A. Bevan for their opinion on the genetics of this family.

References

Bielschowsky, M. (1922). *J. Psychol. Neurol.* (*Lpz.*), **29**, 182.
Cooper, E. L. (1936). *Brit. med. J.*, **1**, 793.
De Bruyn, R. S., and Stern, R. O. (1929). *Brain*, **52**, 84.
Dejerine, J., and Sottas, J. (1893). *C.R. Soc. Biol.* (*Paris*), 9 ser., **5**, 63.
François, J., and Descamps, L. (1949). *Acta neurol. psychiat. belg.*, **49**, 648.
Russell, W. R., and Garland, H. G. (1930). *Brain*, **53**, 376.
Sloane, P. (1939). *J. nerv. ment. Dis.*, **90**, 429.
Snyder, L. H. (1941). *Medical Genetics*. Duke University Press, Durham, North Carolina.
Tooth, H. H. (1886). *The Peroneal Type of Progressive Muscular Atrophy*. Lewis, London.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 52.

GROWTH OF THE SKULL IN YOUNG CHILDREN

PART I: STANDARDS OF HEAD CIRCUMFERENCE

BY

C. K. WESTROPP and C. R. BARBER

From the Social Medicine Unit, University of Oxford

In adults only gross pathological lesions cause an increase in size of the head, but in children enlargement due to slowly growing intracranial lesions must be distinguished from the changes which accompany normal growth. Hence the clinical importance of establishing "normal" increments for each phase of the growing period.

The following contribution to the subject of head size is based on serial measurements of the head circumference of 331 boys and 333 girls who attended the Oxford Child Health Survey between 1944 and 1954.* These children were seen five times during their first year and thereafter at six-monthly intervals until they reached the age of 5 years. An additional appointment at 7 years of age was obtained in nearly 400 cases. In the following account all measurements for the period 1 to 12 months were taken within 14 days of the stated age; from 1 to 5 years they were taken within one month and at 7 years within two months. Failure to reach the age of 7 by 1954, and missed or incorrectly dated appointments account for the different numbers examined at each age and each interval (Tables I and II). The shortest sequence of correctly dated measurements was four and the longest 14. The head circumferences were measured by placing the tape on the supra-orbital margins and carrying it horizontally round the most prominent part of the occiput.

Results

At each of the 14 ages represented in the survey the mean values for boys of the head circumference was a fraction larger than the mean value for girls (Table I). Though invariably slight this difference was greater before the age of 3 (range 1·17 to 0·79 cm.) than after (range 0·85 to 0·45 cm.). That is to say the boys, as usual, began by growing faster than the girls and ended by growing more slowly but at no time did they lose their initial lead. Table II shows the actual increase in head circumference achieved during the period of maximum growth, i.e., 1 month to 3 years. In Table II the sexes are not distinguished but in addition to the means and standard deviations for successive periods, a set of figures is given which indicate the upper limit of "normal" increment. Each of these upper limits represents the mean plus the standard

TABLE I

HEAD CIRCUMFERENCE FOR BOYS AND GIRLS DURING THE FIRST SEVEN YEARS OF LIFE

Age	Boys			Girls		
	Number	Mean (cm.)	S.D.	Number	Mean (cm.)	S.D.
1 month	295	37·3	±1·54	282	36·5	±1·41
3 ,,	229	40·7	±1·43	230	39·8	±1·39
6 ,,	275	43·6	±1·45	262	42·5	±1·42
9 ,,	247	45·7	±1·40	259	44·6	±1·41
1 year	289	46·8	±1·40	275	45·6	±1·22
1½ ,,	255	47·9	±1·40	255	47·0	±1·30
2 ,,	264	49·1	±1·47	260	48·0	±1·32
2½ ,,	219	49·8	±1·39	221	48·8	±1·35
3 ,,	216	50·4	±1·35	227	49·5	±1·35
3½ ,,	226	51·0	±1·40	222	50·1	±1·45
4 ,,	233	51·2	±1·41	229	50·7	±1·46
4½ ,,	220	51·6	±1·45	217	51·0	±1·48
5 ,,	224	51·8	±1·47	225	51·2	±1·50
7 ,,	187	52·7	±1·48	194	52·2	±1·37

TABLE II

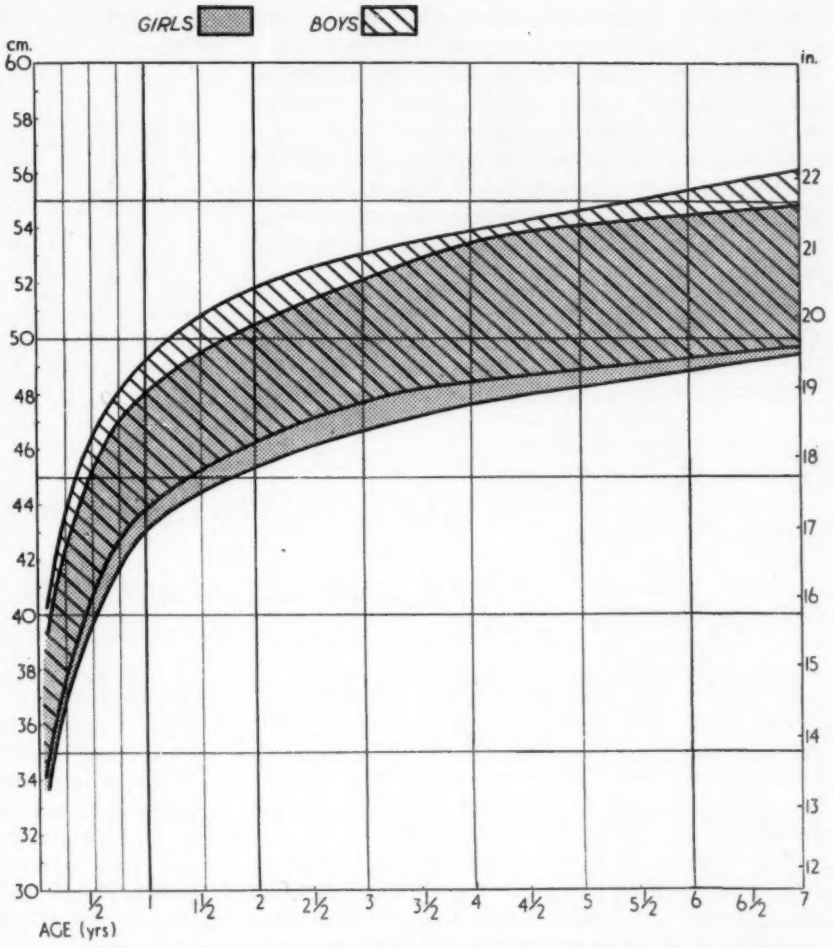
INCREMENTS OF HEAD CIRCUMFERENCE IN FIRST THREE YEARS OF LIFE (BOYS AND GIRLS COMBINED)

Age Period	Number	Mean (cm.)	S.D.	Upper Limit for "Normal" Increments (cm.)
1– 3 months	390	3·4	±1·21	5·7
3– 6 ,,	427	3·2	±1·04	5·2
6–12 ,,	457	3·2	±1·15	5·4
12–18 ,,	442	1·5	±0·81	3·1
18–24 ,,	470	1·2	±0·76	2·7
24–30 ,,	412	0·9	±0·69	2·3
30–36 ,,	397	0·8	±0·67	2·2

* The aims and methods of this survey have already been described (Stewart and Russell, 1952) and an up-to-date list of published papers is available in the bibliography of a recent report (Acheson, Kemp, and Parfit, 1955). Twins were not included but 102 families were represented by two or more sibs. The children were drawn from all levels of society in Oxford but compared with the country as a whole their standard of living was above average (Barber and Blaschko, 1954). Growth changes in the pituitary fossa and anterior fontanelle have formed the subjects of previous papers (Acheson, 1954; Acheson and Jefferson, 1954). Though the survey officially ceased in 1954 a number of children still remain under observation. It is hoped that the serial measurements of head circumference will eventually be available for the age period 7 to 15 years.

deviation multiplied by 1·96 and thus includes nearly all the original measurements. It will be seen that the rate of growth fell rapidly at first and then more slowly, so that what was "normal" for the first two months of observation was also "normal" for the next three months, for the next six months, and for the last 18 months.

Besides revealing a remarkably even progression of the means, Table I shows that the observed variation of the individual measurements was virtually the same in each of the 28 groups defined by age and sex. These two features of the records can be more clearly visualized in the Figure, where provisional ranges of "normal" growth are depicted for the two sexes. In this diagram the records for boys and girls have been superimposed so that the upper margins of the shaded zones represent the lines drawn between serial values of the mean head circumference plus their standard deviations multiplied by 1·96 ($M + 1{\cdot}96\sigma$) and the lower margins the lines between serial means minus $1{\cdot}96\sigma$. In this way the two channels of "normal" growth cover all but 5% of the original measurements. It will be seen that for both sexes 80% of the total growth between 1 month and 7 years was usually achieved by the age of 30 months.



FIGURE—Normal channel of growth of head circumference. (Mean ± 1·96 σ.)

Comparison with Other Published Standards for British Children

Until 1952 standards of head size for British children appear to have been based not on serial measurements of the same children, but on single measurements of children of different ages. The largest series of such head circumferences describes 1,400 children seen at a children's hospital in London (Myers, 1926). Means and ranges for successive age periods are given and the author states that some of the children were measured more than once. The two sexes are distinguished in the Table but the actual number of records is not stated. When plotted in sequence Myer's figures produce an uneven curve, and after the age of 2½ the children he examined appear to have distinctly smaller heads than the Oxford children.

Textbooks of children's diseases often include a table of "normal" head circumference for different ages (Pearson and Wyllie, 1935; Paterson, 1944; Sheldon, 1951; Grulee and Eley, 1952; Moncrieff and Evans, 1953). It is frequently impossible to discover on what these standards are based, but they all have one thing in common: when plotted as growth curves they yield an uneven sequence, thus betraying the fact that they are not based on serial measurements of the same children.

The first longitudinal growth study of British children of pre-school age was published in 1952 (Low). This describes 66 boys and 60 girls, born in Aberdeen between 1923 and 1927, and measured at yearly intervals during the period 3 days to 5 years. At all ages these children were lighter,

shorter, and had smaller heads than the Oxford children. Nevertheless the sex differences in head circumference, the smoothness and general shape of the head growth curves, and the range of variation in the individual measurements are strictly comparable in the two series. It is a moot point whether the differences in absolute size are racial in origin, or whether they are due to secular changes in body size (Clements, 1953), or to different standards of nutrition.

We are indebted to Miss McLarty (Radcliffe Infirmary) for the Figure and to our colleagues Dr. Acheson and Dr. Alice Stewart for much constructive advice. The Nuffield Provincial Hospitals Trust and the Medical Research Council covered the expenses of the investigation.

References

Acheson, R. M. (1954). *Brit. J. Radiol.*, **27**, 298.
——, and Jefferson, E. (1954) *Arch. Dis. Childh.*, **29**, 196.
——, Kemp, F. H., and Parfit, J. (1955). *Lancet*, **1**, 691.
Barber, R., and Blaschko, M. (1954). *Med. Offr.*, **91**, 5.
Clements, E. M. B. (1953). *Brit. med. J.*, **2**, 897.
Grulee, C. G., and Eley, R. C. (1952). *The Child in Health and Disease*, 2nd ed. Williams and Wilkins, Baltimore.
Low, A. (1952). *Growth of Children*. University of Aberdeen.
Moncrieff, A., and Evans, P. (1953). Garrod, Batten and Thursfield's *Diseases of Children*, 5th ed. Arnold, London.
Myers, B. (1926). *Brit. J. Child. Dis.*, **23**, 87.
Paterson, D. (1944). *Sick Children*, 5th ed. Cassell, London.
Pearson, W. J., and Wyllie, W. G. (1935). *Recent Advances in Diseases of Children*, 3rd ed. Churchill, London.
Sheldon, W. (1951). *Diseases of Infancy and Childhood*, 6th ed. Churchill, London.
Stewart, A. M., and Russell, W. T. (1952). *Med. Offr.*, **88**, 5.

PART II: CHANGES IN HEAD SHAPE

BY

C. R. BARBER and D. HEWITT

From the Social Medicine Unit, University of Oxford

In Part I the increase in head circumference which occurs during the first seven years of life is described; Part II is based on the same children and compares the contributions made by growth in the transverse and longitudinal diameters to the overall increase in head circumference.

The "transverse skull diameters" correspond to caliper readings of the maximum distance between the parietal eminences, and the "longitudinal diameters" to caliper readings of the maximum distance between the frontal and occipital eminences. These two measurements were taken five times during the first year, and thereafter at six-monthly intervals to the age of 5 with one additional measurement at 7 years. On average, just under 300 children of each sex were measured at each age.

Mean values for the transverse and longitudinal diameters by sex and age are shown in Table I and Fig. 1. In both diameters and at each age the boys' heads were significantly larger than the girls', but the mean differences never exceeded 0·5 cm. and the total increments for the whole seven-year period were virtually identical in the two sexes. (The boys actually gained 1 mm. less in the transverse and 1 mm. more in the antero-posterior diameter.) In both sexes, but particularly in girls,

TABLE

MEAN TRANSVERSE AND LONGITUDINAL SKULL DIAMETERS AND CEPHALIC INDICES OF OXFORD BOYS AND GIRLS AGED 1 MONTH TO 7 YEARS

Age	Boys						Girls					
	No.	Transverse		Longitudinal		Cephalic Index	No.	Transverse		Longitudinal		Cephalic Index
		Mean (cm.)	S.D.	Mean (cm.)	S.D.			Mean (cm.)	S.D.	Mean (cm.)	S.D.	
1 month	297	10·2	±0·62	13·0	±0·80	78·6	299	9·8	±0·54	12·7	±0·76	77·5
3 months	308	11·0	±0·49	13·9	±0·71	79·5	307	10·9	±0·53	13·7	±0·77	79·8
6 ,,	310	12·0	±0·64	14·8	±0·77	81·3	317	11·8	±0·56	14·7	±0·81	80·4
9 ,,	284	12·6	±0·59	15·5	±0·69	81·3	298	12·4	±0·59	15·4	±0·78	80·8
12 ,,	332	12·9	±0·58	16·0	±0·75	80·9	331	12·8	±0·54	15·9	±0·83	80·5
1½ years	318	13·2	±0·58	16·6	±0·70	79·6	329	13·0	±0·54	16·3	±0·68	79·8
2 ,,	328	13·5	±0·59	17·0	±0·72	79·5	325	13·2	±0·51	16·7	±0·66	79·2
2½ ,,	283	13·8	±0·55	17·3	±0·69	79·8	295	13·5	±0·51	16·9	±0·69	79·6
3 ,,	281	13·8	±0·56	17·3	±0·70	79·6	290	13·6	±0·53	17·0	±0·65	80·0
3½ ,,	268	13·9	±0·57	17·6	±0·65	79·1	272	13·7	±0·53	17·2	±0·59	79·6
4 ,,	269	14·0	±0·56	17·7	±0·62	79·1	267	13·8	±0·50	17·3	±0·60	79·6
4½ ,,	250	14·1	±0·54	17·9	±0·60	78·8	256	13·9	±0·51	17·4	±0·60	79·6
5 ,,	260	14·1	±0·56	18·0	±0·59	78·7	265	13·9	±0·52	17·5	±0·58	79·3
7 ,,	186	14·4	±0·55	18·2	±0·61	79·4	199	14·1	±0·53	17·8	±0·63	79·6

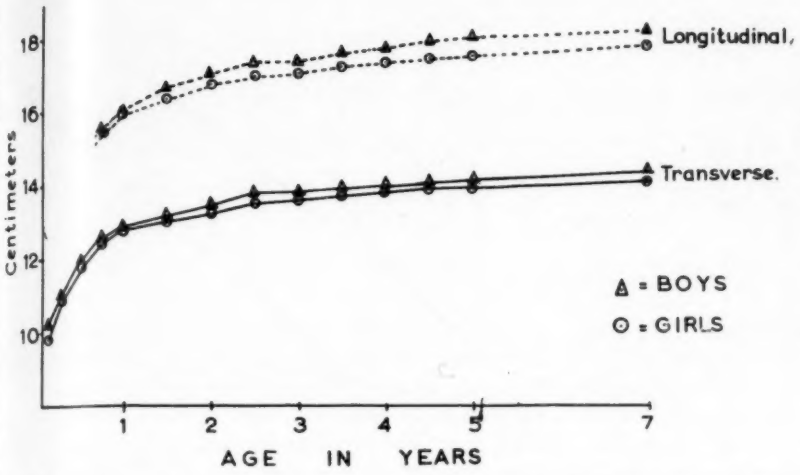


FIG. 1.—Mean transverse and longitudinal skull diameters of Oxford children by sex and age.

the percentage increase over the seven-year period was slightly greater for the transverse than for the longitudinal diameter.

This last finding implies that the girls, and to a lesser extent the boys, were more brachycephalic at the age of 7 than they were at birth. It was decided therefore to establish, for each sex, the relations between age and cephalic index i.e.,

$$\frac{\text{Transverse diameter}}{\text{Longitudinal diameter}} \times 100,$$

thus in Table 1 and Fig. 2* it will be seen that in both sexes the cephalic index increased rapidly during the first six months of life and achieved a maximum value shortly before the age of 9 months. Thereafter there was a difference between the two sexes. Thus the index for boys declined fairly rapidly and by the age of 5 had almost regained its original level. For the girls, however, the ratio of breadth to length declined more slowly, and by 3 years of age these children were already showing the relatively brachycephalic skull which is, in adult life, characteristic of the female sex.

It appears, therefore, that the mechanism that controls the increase in skull size during childhood is far from simple. Thus (i) the longitudinal and transverse diameters do not grow at the same rate; (ii) the difference between their rates of growth undergoes an abrupt change between the sixth and ninth month; and (iii) this change is more marked in boys than in girls and is responsible for a sex difference in head shape.

Huxley (1932) has made intensive studies of comparable growth phenomena and shown that an empirical rule governs such situations. This so-called law of allometric growth may be stated as follows. Let B and L represent two cognate measurements of a growing body (in this case breadth and length of skull). The instantaneous growth rates of these measurements may be written as $\frac{dB}{B}$ and $\frac{dL}{L}$ and we may define a coefficient b as $b = \frac{dB}{B} \cdot \frac{L}{dL}$. This coefficient, which is sometimes known as the "growth partition coefficient", is often found to have a constant value throughout each of a small number of distinct "phases" in the growth of the body. Provided, therefore, that the law applies to the particular case, it is only necessary to plot the logarithms of B and L against one another for it to become apparent that the points lie close to (say) two straight

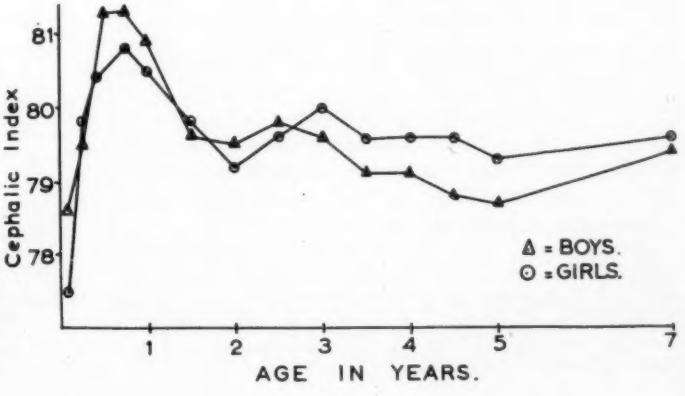


FIG. 2.—Cephalic index of Oxford children by sex and age.

Cephalic Index
77·5
79·8
80·4
80·8
80·5
79·8
79·2
79·6
80·0
79·6
79·6
79·6
79·3
79·6

* The points plotted in this figure are derived from the mean diameters at each age and are therefore not identical with the mean cephalic indices, though they certainly follow the same course with respect to age. Estimates were also made, for each age, of the standard deviation of the cephalic index, from which it appeared that the range of fluctuation shown in Fig. 2 was eight to 10 times as great as the standard error of a mean index based on 300 children.

lines, the slopes of which are equivalent to the coefficient b as defined above.

The logarithms of skull breadth and length at each of the 14 ages are plotted for boys and for girls in Fig. 3, and it is clear that for each sex the distribution of points accords with expectations based on the law of allometric growth. To obtain estimates of b, the whole period was divided into two parts which, according to the graph, appeared to represent different phases of growth. The first of these runs from 1 to 9 months, i.e., covers four points on the graph, and the second, 1 year to 7 years, i.e., covers 10 points. Straight lines were then fitted to each set of points by the method of least squares† and the values of b obtained (see Table).

It is particularly interesting to note that the growth partition coefficients for the first nine months turned out to be identical for the two sexes.

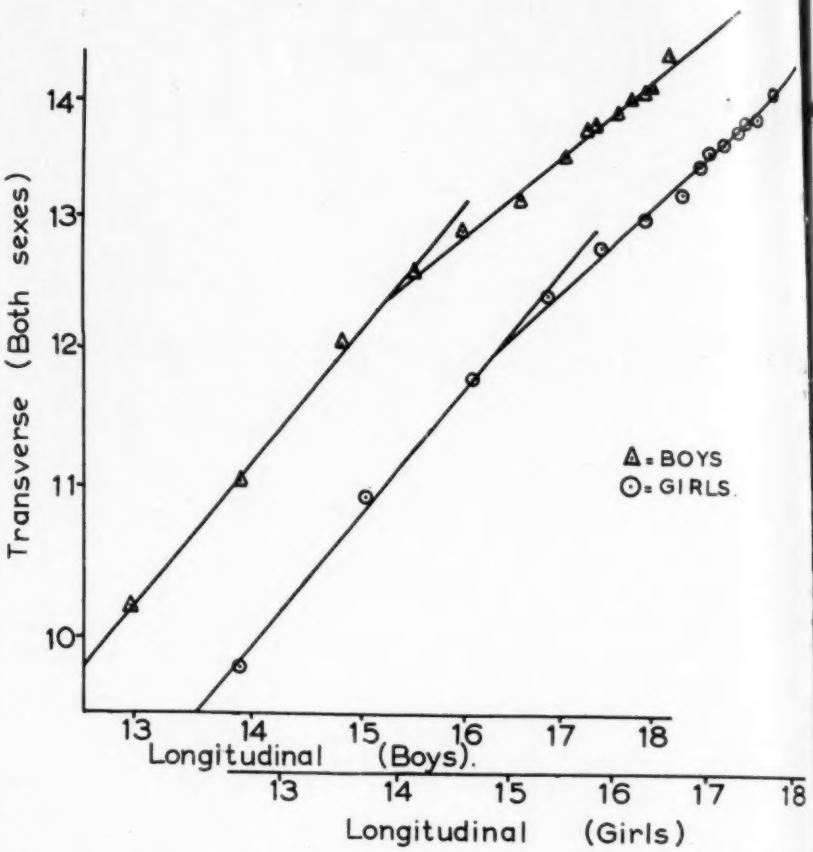


FIG. 3.—Comparative growth of longitudinal and transverse diameters of the skull in Oxford boys and girls aged 1 month to 7 years.

	Sex	1 month–9 months	1 year–7 years
Growth partition Coefficients (b)	Boys	1·21	0·84
	Girls	1·21	0·92

Comparison with Other Surveys

The results of two other longitudinal growth surveys are available for comparison with the Oxford children, one describing American and the other Scottish children (Simmons, 1944; Low, 1952). In all three surveys the mean skull diameters are slightly greater for boys than for girls, but compared with the two British series, the American children have rather small, brachycephalic heads. In all three groups the mean cephalic indices are greater for girls than for boys and reach peak values before 12 months.

† Cawley, Waterhouse, and Hogben (1949), in a similar study, advocate a fitting procedure in which the perpendicular deviations are minimized. The need for this did not arise in the present case since the smallest of the four correlation coefficients was +0·992 and hence the slopes of the conventional regression lines were indistinguishable.

Summary

The growth of the skull during early childhood may be divided into two phases. During the first of these the rate of increase of the transverse diameter exceeds that of the longitudinal diameter by approximately 20% and both boys and girls become increasingly brachycephalic. During the third trimester of post-natal life a second phase is initiated in which the growth rate of the transverse diameter is less than that of the longitudinal diameter. By the end of the first year this trend towards dolichocephaly (which is more marked in boys than in girls) is firmly established.

REFERENCES

Cawley, R. H., Waterhouse, J. A. H., and Hogben, H. (1949). *Brit. J. Soc. Med.*, 3, 157.
Huxley, J. S. (1932). *Problems of Relative Growth.* Methuen, London.
Low, A. (1952). *Growth of Children.* University of Aberdeen.
Simmons, K. (1944). The Brush Foundation Study of Child Growth and Development 2. Physical Growth and Development. *Monogr. Soc. Res. Child Dev.*, 9, No. 1.
Westropp, C. K., and Barber, C. R. (1955). *Journal of Neurology, Neurosurgery and Psychiatry*, 19, 52.

J. Neurol. Neurosurg. Psychiat., 1956, 19, 57.

ALTERED RESPONSE TO SMALL DOSES OF INSULIN ASSOCIATED WITH ELECTROPLEXY AND HYPOGLYCAEMIC THERAPIES *

BY

E. MARLEY

From Severalls Hospital, Colchester

The measurement of response to insulin utilizes a number of qualitative and quantitative variables. For example, in the treatment of diabetes there are varying criteria as to what constitutes satisfactory control of the disorder, whereas with deep insulin treatment for schizophrenia in which the end-point is the production of coma, the variables include the definition of coma, the degree of resistance to the drug, and the possibility that the nervous system of each individual treated shows its own selective susceptibility to insulin as it does to many other drugs (Kalinowsky and Hoch, 1952).

Fortunately, the response to small doses of insulin can be determined more precisely by the use of the insulin tolerance test, and the results reported in this paper derive from sequential insulin tolerance tests on psychotic and neurotic patients receiving either deep or modified insulin, or electroplexy (E.C.T.). However, not even this assessment of response to insulin is devoid of controversy, for, although the conventional procedure requires the calculation of the test dose in terms of the body weight, doubt as to the validity of the strict adjustment of dosage to body weight has been expressed by Somogyi (1949). Tests were performed before, during, and after treatment, and the results that accrued were validated statistically.

This technique of using the patient as his own control in the comparison of sequential tests has much to recommend it, variations due to differences in responsiveness between patients being eliminated (Reid, 1954), but the inconstancy of physiological equilibrium in schizophrenic disorders has been emphasized by Hemphill and Reiss (1948), who cautioned that if biochemical investigations such as the insulin tolerance and the sugar tolerance tests were repeated frequently in these patients, much day-to-day variation in results became evident. This is not the only factor that may introduce an error into the results, for Hubble (1954) demonstrated phasic insulin resistance in a young diabetic girl. He found that the insulin-resistant phases were usually pre-menstrual and the insulin-sensitive phases post-menstrual. Other workers had previously shown that oestrogens are diabetogenic, whereas androgens have a contrary effect (Houssay, 1951). It is for reasons such as these that the only patients included in this series are males.

Although there have been many investigations into the possibility of a relation between the results of insulin tolerance tests and the dose of insulin required to produce coma (Kaplan and Low, 1939; Harris, 1942; Borenz, Schuster, and Downey, 1949), the only reported results that I have been able to discover comparing the results of insulin tolerance tests before deep insulin therapy with those obtained either during or immediately after the termination of treatment derive from Borenz and others (1949) who comment on the lack of any constant change in the test results after therapy apart from some slight increased tolerance to small doses of insulin. There is a similar paucity of literature concerning any variation in the response to small doses of insulin following the administration of E.C.T., but Delay and Soulairac (1944) have observed that the hyperglycaemia produced by electro-shock is singularly resistant to insulin, a finding that has been confirmed by others (Marley, 1952).

Methods

The technique adopted for the insulin tolerance test was that proposed by Fraser, Albright, and Smith (1941) who recommend the intravenous administration of 0·1 unit of insulin per kilogram of ideal body weight. As the previous diet influences the response to insulin (Himsworth, 1935), the patients were given at least 300 g. carbohydrate daily for three days before the test. All patients came to the ward at 7.30 a.m. and remained at rest in bed until the test began at approximately 9 a.m. when they had then been fasting for 12 hours. Capillary blood was first withdrawn for the estimation of the fasting blood sugar, after which the insulin was injected. At 20, 30, 45, 60, 90, and 120 minutes afterwards further samples of blood were taken.

* Abstracted partly from a thesis accepted for the degree of M.D. Cantab., 1953.

The response of the blood sugar to insulin can be differentiated into two phases: the initial decrease of blood sugar which is indicative of insulin sensitivity, and the secondary rise which is representative of the responsiveness to hypoglycaemia. The difference between the fasting and the 30-minute blood sugar value was adopted as an index of the first function, the mean values for these differences being calculated for the group. As suggested by Fraser and Smith (1941), a measure of the responsiveness to hypoglycaemia was obtained from the product of the percentage blood sugar values at 45, 60, 90, and 120 minutes after the beginning of the test and the time interval of these from the previous sample, a quarter of an hour being taken as unity. These products were then added together and termed the hypoglycaemia responsive index (H.R.I.). Fraser and Smith (1941) claim that this integer is a close approximation to the area enclosed between the insulin tolerance curve and the zero blood sugar line, and is therefore an inverse measure of the degree and persistence of hypoglycaemia after the 30 minutes' sample. The mean H.R.I. obtained from these results was calculated for the group. The limits of the H.R.I. as quoted by these authors varied in the normal from 474 units to 621 units, with a mean of 550 units.

As the results of insulin tolerance tests repeated at short intervals were being compared, it was essential to show that repeated tests under standard circumstances manifested no significant statistical dissimilarity. This was done, and it was seen that even in schizophrenics the results of insulin tolerance tests repeated at short intervals were strictly comparable (Marley, 1953a). Patients were therefore tested within 10 days of beginning treatment, between the fifth and twelfth days of treatment, between the thirteenth day and the end of treatment, and again within 10 days after the completion of therapy. In the case of those tests performed during the course of treatment, patients were rested from the latter for three days before testing not only to ensure that the strictures as regards diet were obeyed but also to exclude any immediately preceding effect of recent therapy.

The blood sugars were estimated by the method devised by Herbert and Bourne (1930), which is a determination of the true blood glucose.

No patient was accepted for testing if he was markedly underweight, as it has been demonstrated that changes attributable to the general adaptation syndrome are constantly present in association with severe malnourishment (Selye, 1950a). For the same reason, patients treated in the two months before the investigation with either E.C.T. or deep or modified insulin were rejected (Gellhorn and Safford, 1948; Henneman, Altschule, and Siegel, 1951).

Results

The results of insulin tolerance tests on 20 psychotic patients treated with deep insulin, five psychotics treated with E.C.T., and seven patients suffering from neurotic illnesses treated with modified insulin were analysed and compared statistically. There were, of course, individual exceptions to the mean results reported later in the paper, but these have not been abstracted from the context as it was considered that the analysis of group changes was more informative.

The patients were all males, those suffering from psychoses being diagnosed as having schizophrenia.

The mean values, and their standard deviations, derived from the results of insulin tolerance tests are presented in Table I. It can be seen that the mean fall of blood sugar following the administration of small doses of insulin was increased during and immediately after the cessation of treatment with either deep or modified insulin, but only during and not after E.C.T. The maximum fall of blood sugar occurred on testing between the fifth and the twelfth days of therapy with deep insulin or E.C.T., and between the thirteenth day and the end of treatment for those patients having modified insulin. The mean H.R.I. for the different groups showed a progressive decline during and after all therapies.

The significance of the differences between these mean values has been assessed statistically and presented in Table II. The means compared were those obtained before treatment and those found between the fifth and twelfth days of therapy

TABLE I

MEAN AND S.D. VALUES DERIVED FROM INSULIN TOLERANCE TESTS ON PATIENTS TREATED WITH DEEP AND MODIFIED INSULIN AND E.C.T.

Indices	Before Therapy	5th–12th Day of Therapy	13th Day to End of Therapy	After Therapy
Patients treated with deep insulin				
Fall of blood sugar (mg.)	40·8 ± 7·41	47·0 ± 9·63	45·3 ± 11·11	46·4 ± 8·13
Fall of blood sugar (%)	53·6 ± 6·44	57·9 ± 10·10	55·4 ± 12·21	57·3 ± 8·75
H.R.I.	498·6 ± 59·36	452·0 ± 42·15	462·1 ± 44·40	417·6 ± 43·46
Patients treated with modified insulin				
Fall of blood sugar (mg.)	40·7 ± 5·47	45·0 ± 5·49	46·2 ± 11·84	45·4 ± 19·67
Fall of blood sugar (%)	54·3 ± 4·77	57·1 ± 4·73	56·2 ± 10·27	54·8 ± 18·69
H.R.I.	550·7 ± 63·07	491·4 ± 53·44	464·2 ± 48·32	453·7 ± 80·73
Patients treated with E.C.T.				
Fall of blood sugar (mg.)	42·8 ± 7·05	49·2 ± 6·22	48·6 ± 5·18	42·0 ± 11·56
Fall of blood sugar (%)	58·4 ± 5·31	62·4 ± 7·54	59·6 ± 6·39	56·8 ± 9·09
H.R.I.	464·6 ± 8·29	437·0 ± 13·22	418·4 ± 16·34	413·2 ± 21·85

(Series 1 and 2), the means before treatment and those between the thirteenth day and the cessation of therapy (Series 1 and 3), and those obtained before and after treatment (Series 1 and 4).

TABLE II

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS DERIVED FROM TESTS ON PATIENTS TREATED WITH DEEP AND MODIFIED INSULIN AND E.C.T.

Indices	Statistical Criteria	Series 1 and 2	Series 1 and 3	Series 1 and 4
Patients treated with deep insulin				
Fall of blood sugar (mg.)	t	2·40	1·53	2·22
	P	<0·01	>0·05	<0·025
	significance	+	−	+
Fall of blood sugar (%)	t	1·79	0·54	1·51
	P	<0·05	>0·25	>0·05
	significance	+	−	−
H.R.I. ..	t	2·77	2·10	4·47
	P	<0·005	<0·025	<0·005
	significance	+	+	+
Patients treated with modified insulin				
Fall of blood sugar (mg.)	t	1·36	1·10	0·61
	P	>0·05	>0·10	>0·25
	significance	−	−	−
Fall of blood sugar (%)	t	1·02	0·41	0·07
	P	>0·10	>0·30	>0·45
	significance	−	−	−
H.R.I. ..	t	1·76	2·54	1·98
	P	>0·05	<0·025	<0·025
	significance	−	+	+
Patients treated with E.C.T.				
Fall of blood sugar (mg.)	t	1·52	1·50	0·01
	P	>0·05	>0·05	>0·45
	significance	−	−	−
Fall of blood sugar (%)	t	0·97	0·37	0·34
	P	>0·15	>0·35	>0·35
	significance	−	−	−
H.R.I. ..	t	3·36	4·85	4·30
	P	<0·01	<0·005	<0·005
	significance	+	+	+

From Table II it can be seen that the mean hypoglycaemic effect of small doses of insulin is significantly increased during the early phases of deep insulin therapy. The mean fall of blood sugar in the groups treated with modified insulin or E.C.T. is similarly augmented, although in these the fall is not significant. Similarly there is a significant decline in the mean values for the H.R.I. obtained on testing with small doses of insulin during and after all therapies, the one exception being the insignificant decline of the mean H.R.I. associated with testing between the fifth and twelfth days of treatment with modified insulin. It is worthy of note that the mean values for the H.R.I. derived from these tests were frequently lower than the minimum of the range of normal values for the H.R.I. reported by Fraser and Smith (1941).

Another interesting feature is that whilst the hypoglycaemic effect of small doses of insulin was most increased between the fifth and twelfth days of deep insulin therapy and the value for the H.R.I. least decreased, the mean dose of insulin required at this time to produce or attempt to produce coma was 317·7 units. Although this augmented hypoglycaemic effect of small doses of insulin was not so evident on testing towards the completion of a course of deep insulin and the mean value for the H.R.I. had further decreased, the mean dose of insulin given at this time to produce or attempt to produce coma was still as high as 276·6 units.

Discussion

The results presented above show that for the groups as a whole there was an increase in the hypoglycaemic effect of small doses of insulin during or after treatment, no matter whether therapy was with insulin or E.C.T. As resistance to the hypoglycaemic effect of insulin depends on the activity of the anterior pituitary and adrenal cortical hormones (Bouckaert and de Duve, 1947), presumably this augmented hypoglycaemic response represents some alteration in the requirements or activity of these hormones.

A similar phenomenon was reported by Masson (1941). He found that rats continuously treated by exposure to cold, forced muscular exercise, or with injections of formaldehyde, after 24 hours, that is, during what he considered to be the " alarm stage " of Selye's general adaptation syndrome, manifested a small and perhaps insignificant decrease in the hypoglycaemic action of insulin. However, during the " stage of resistance " of this syndrome, that is, after nine days of such treatment, the hypoglycaemic action was considerably increased. Thus, both on the sixth and ninth days of exposure to these three noxious agents, the identical dose of insulin consistently produced a particularly severe drop in the blood sugar. He surmised, therefore, that the hypoglycaemic action of this hormone increases as the animal adapts itself to the non-specific damaging agents. In addition, the increased insulin tolerance seen in patients during the immediate post-operative period after lumbo-dorsal sympathectomy is followed by a secondary stage of increased sensitivity to the drug. This alteration in insulin resistance has been interpreted as a manifestation of the general adaptation syndrome (Simeone and Vavoudes, 1948 ; Simeone, 1949). The non-specific effect of E.C.T. has been commented on by Roth and Rosie (1953) and in the same manner insulin has a non-specific action besides its effect on the blood sugar (Paschkis, Cantarow, Walkling, and Boyle, 1950). Presumably, then, this altered hypoglycaemic response to small doses of insulin reflects an adaptation on the part of the body to the repeated administration of large doses of insulin or the repeated application of E.C.T. It is this phase of optimal adaptation that Selye has termed the " stage of resistance " of the general adaptation syndrome (Selye, 1946).

The mean values for the H.R.I. were significantly reduced both during and after treatment, and as responsiveness to hypoglycaemia depends on the action of adrenal cortical hormones and efficient gluconeogenesis, the unresponsiveness can be equated once more in terms of altered activity of the adrenal cortex. Furthermore, as the mean fall of blood sugar was in all instances greater than 50% of the mean values for the fasting blood sugars, the unresponsiveness could not be attributed to an inadequate stimulation of the blood sugar raising mechanisms.

The results of these tests would therefore seem on first impressions to imply an inadequate response of the anterior pituitary and adrenal cortex during and immediately after the completion of treatment, but any actual deficiency of these particular endocrines is readily excluded by the fact that those patients receiving hypoglycaemic therapy still required large doses of insulin for the production of satisfactory comas. An explanation of this paradox becomes feasible when it is recognized that the blood steroid levels are significantly elevated during treatment with deep insulin or E.C.T. (Bliss, Migeon, Nelson, Samuels, and Hardin Branch, 1954), and that the steroids include the group of 11-oxycorticosteroids, one of which is cortisone. Sayers and Sayers (1947) have suggested that its release inhibits the production of A.C.T.H. by the pituitary, and further considered that its inhibition was self-regulatory inasmuch as the pituitary secretes A.C.T.H. at a rate which is adjusted to the requirements of the peripheral tissues. But the action of small doses of insulin is mainly peripheral (Bouckaert and de Duve, 1947) as is also the antagonistic effect of adrenal cortical hormones on carbohydrate metabolism (Bondy, 1949). Thus, the results of insulin tolerance tests measure preponderantly the peripheral anti-insulin activity, whereas the larger doses of this hormone, such as are employed during deep insulin therapy, act mainly on the liver (Bouckaert and de Duve, 1947). Presumably then adaptation to the continued injection of large doses of insulin alters the peripheral requirements for corticoids and so modifies the response to small doses of the substance. A similar rationale must apply to the diminished response with sequential insulin tolerance tests accompanying the repeated application of E.C.T.

These findings are reminiscent of the work of Last, Jordan, Pitesky, and Siegel (1950) who excluded exhaustion of either the anterior pituitary or the adrenal cortex during an investigation of adaptation to epinephrine stress. They therefore suggested that adaptation to stress implied a decreased utilization of corticoids and consequently a decreased stimulus for the production of A.C.T.H. Finally, it seems relevant to include the view sponsored by Selye (1950b), who maintained that during the stage of resistance of the general adaptation syndrome carbohydrate metabolism readjusts itself so that the adrenal hormones become less important in the maintenance of the blood sugar level. In the terms of this interpretation, the repeated administration of large doses of insulin or E.C.T. results in a readjustment of carbohydrate metabolism revealed in serial tests with small doses of insulin.

Other tissue and biochemical deviations that accompany these therapies and seem also to represent non-specific adaptation have been formulated elsewhere (Marley, 1953b).

Summary

The mean hypoglycaemic effect of small doses of insulin is significantly increased during the early phases of deep insulin therapy. The mean fall of blood sugar after small doses of insulin is similarly but insignificantly augmented in the groups treated with modified insulin or E.C.T. This increased hypoglycaemic effect persisted for a short time after the termination of deep or modified insulin but not after E.C.T.

There is a significant decline in the mean values for the hypoglycaemia responsive index during and after all therapies.

These changes seem to imply a decreased peripheral requirement for corticoids and to represent an adaptation on the part of the body to the repeated administration of large doses of insulin or the repeated application of E.C.T.

Exhaustion of either the anterior pituitary or the adrenal cortex was excluded in the case of those patients being treated with deep insulin.

I should like to take this opportunity of thanking Dr. A. G. Duncan, the Medical Superintendent, for his kind permission to publish these findings.

In addition, I should also like to thank Nurse H. Gayler and Nurse G. Gordon for their unstinted assistance and cooperation which facilitated the progress of this investigation.

References

Bliss, E. L., Migeon, C. J., Nelson, D. H., Samuels, L. T., and Hardin Branch, C. H. (1954). *Arch. Neurol. Psychiat.* (*Chicago*), 72, 352.

Bondy, P. K. (1949). *Endocrinology*, **45**, 605.

Borenz, H. F., Schuster, D. B., and Downey, G. J. (1949). *J. nerv. ment. Dis.*, **110**, 507.

Bouckaert, J. P., and de Duve, C. (1947). *Physiol. Rev.*, **27**, 39.

Delay, J., and Soulairac, A. (1944). *C. R. Soc. Biol.*, (*Paris*), **138**, 490.

Fraser, R., and Smith, P. H. (1941). *Quart. J. Med.*, **10**, 297.

——, Albright, F., and Smith, P. H. (1941). *J. clin. Endocr.*, **1**, 297.

Gellhorn, E., and Safford, H. (1948). *Proc. Soc. exp. Biol.* (*N.Y.*), **68**, 74.

Harris, M. M. (1942). *Arch. Neurol., Psychiat.* (*Chicago*), **48**, 761.

Hemphill, R. E., and Reiss, M. (1948). *Proc. roy. Soc. Med.*, **41**, 533.

Henneman, D. H., Altschule, M. D., and Siegel, E. (1951). *J. appl. Physiol.*, **3**, 411.
Herbert, F. K., and Bourne, M. C. (1930). *Biochem. J.*, **24**, 299.
Himsworth, H. P. (1935). *Clin. Sci.*, **2**, 67.
Houssay, B. A. (1951). *Brit. med. J.*, **2**, 505.
Hubble, D. (1954). *Ibid.*, **2**, 1022.
Kalinowsky, L. B., and Hoch, P. H. (1952). *Shock Treatments, Psychosurgery and other Somatic Treatments in Psychiatry*, 2nd ed., p. 13. Grune and Stratton, New York.
Kaplan, M., and Low, A. A. (1939). *Amer. J. Psychiat.*, **96**, 689.
Last, J. H., Jordan, P. H., Pitesky, I., and Siegel, B. M. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, **74**, 96.
Marley, E. (1952). Unpublished data.
——(1953a). M.D. Thesis, p. 50. Cambridge.
Marley, E. (1953b). *Ibid.*, p. 165.
Masson, G. (1941). *Endocrinology*, **29**, 453.
Paschkis, K. E., Cantarow, A., Walkling, A. A., and Boyle, D. (1950). *Ibid.*, **47**, 338.
Reid, D. D. (1954). *Lancet*, **2**, 1293.
Roth, M., and Rosie, J. M. (1953). *J. ment. Sci.*, **99**, 103.
Sayers, G., and Sayers, M. A. (1947). *Endocrinology*, **40**, 265.
Selye, H. (1946). *J. clin. Endocr.*, **6**, 117.
——(1950a). *Stress*, 1st ed., p. 48. Acta, Montreal.
——(1950b). *Ibid.*, p. 124.
Simeone, F. A. (1949). *J. clin. Invest.*, **28**, 810.
——, and Vavoudes, H. (1948). *Surgery*, **24**, 326.
Somogyi, M. (1949). *J. biol. Chem.*, **179**, 217.

THE NOVEMBER (1955) ISSUE

The November (1955) issue contains the following papers :—

The Blood-Cerebrospinal Fluid Barrier in Tuberculous Meningitis and Allied Conditions. H. V. Smith, L. M. Taylor, and G. Hunter.

The Babinski Response : A Review and New Observations. P. W. Nathan and Marion C. Smith.

The Pathological Effects Produced by Sera of Animals Immunized with Foreign Nervous or Splenic Tissue. Part II : Intra-arterial Injection of Serum. E. Weston Hurst.

The Projection of the Midline and Intralaminar Nuclei of the Thalamus of the Rabbit. W. M. Cowan and T. P. S. Powell.

Non-specific Effects of Insulin and Electroplexy. E. Marley.

A Preliminary Report on a Perceptual Maze Test Sensitive to Brain Damage. Alick Elithorn.

Head Injury as a Cause of Internal Carotid Thrombosis. C. B. Sedzimir.

Report of a Family Suffering from Friedreich's Disease, Peroneal Muscular Atrophy, and Schizophrenia. Michael Shepherd.

Localized Enlargement of the Spinal Canal in the Absence of Tumour : A Congenital Abnormality. Antony Jefferson.

An Electrode Holder for Direct Encephalography with Its Own Sterilizing Cabinet. G. Pampiglione and R. Cooper.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 62.

THE VALUE OF THE MARCHI METHOD FOR STAINING TISSUE STORED IN FORMALIN FOR PROLONGED PERIODS

BY

MARION C. SMITH, SABINA J. STRICH,* and PETER SHARP

From the National Hospital for Nervous Diseases, Queen Square, London, and the Radcliffe Infirmary, Oxford

This paper reports the demonstration of degenerating myelin by the Marchi method in material kept in formalin for periods ranging from 22 months to over eight years.

It has generally been believed that prolonged immersion in formalin renders material useless for investigation by the Marchi method, because of the constant occurrence of extensive artefacts. Fourteen days has usually been considered the maximum period during which tissue may be exposed to the action of formalin before making Marchi preparations in order to obtain clear incontrovertible evidence of myelin degeneration. In Marchi preparations the presence of abundant black pseudo-Marchi bodies, or of black staining of normal myelin sheaths, may completely obscure the tissue degeneration.

Bertrand wrote in 1930 :

> " Sur toutes les préparations au Marchi existe une fine poussière de granulations noirâtres sans rapport avec un processus dégénératif quelconque, il nous a semblé que cet aspect était particulièrement marqué après une longue fixation au formol, sur un matériel ancien. Il est même fréquent de voir des gâines de myéline normale noircies sur un segment plus ou moins éxtendu de leur circonférence."

Swank and Davenport (1934) stated : " Prolonged formalin fixation . . . increased the dust." They also showed that prolonged fixation (for one year) causes staining of the normal myelin sheaths. They considered the artefacts caused by formalin fixation to be the result of prolonged action of that fixative on the lipoids. Later, in 1942, Mettler and Hanada wrote : " The brain should never be allowed to fix in formalin alone for more than 24 hours." These are only examples of numerous similar statements. Occasional reference has been made to satisfactory Marchi preparations obtained after rather longer storage in formalin than usual. Poirier, Ayotte, and Gauthier (1954), in a paper describing a modified form of the Marchi method, showed a photograph of clear degeneration in a monkey after 100 days in formalin. But no worker, to our knowledge, has given conclusive evidence that material stored for many months in formalin is still suitable for examination by the Marchi method.

We report here our results with the Marchi method in four cases of head injury. In these patients the interval between injury and death varied between nine and 15 months. The material from these cases had been stored in formol-saline for periods ranging from 22 to 100 months before examination. The period of survival after the lesion, and the period of storage in formol-saline in each case are shown in the Table.

TABLE
PERIODS OF SURVIVAL AND FIXATION

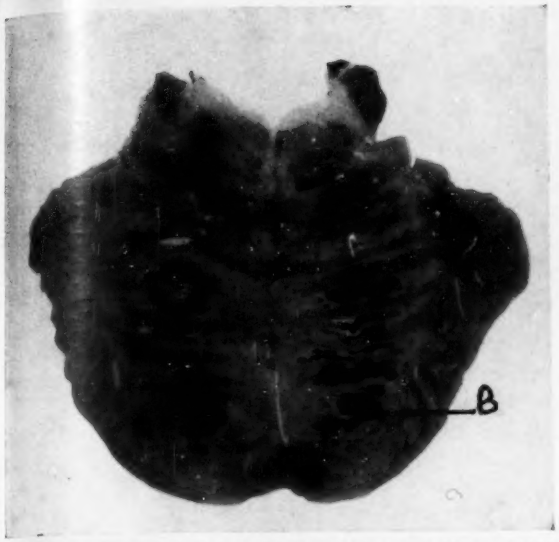
Case	Period of Survival after Lesion (months)	Period of Formalin Fixation (months)
A	9	22
B	11	26
C	15	43
D	12	100

The method employed in staining this old material was essentially that recommended by Swank and Davenport (1934) and modified by Glees (1943). But it was found advantageous to mount some frozen sections without dehydration or clearing, as well as sections which were dehydrated and cleared in the usual manner before mounting. After impregnating the blocks with the osmic acid solution for 10 days, they were washed in running water for 24 to 48 hours ; the length of the washing time depended on the size of the blocks.

Frozen sections were cut 24μ thick and put into distilled water. The sections were either mounted directly in glycerine jelly without clearing, or dehydrated, cleared in cedar wood oil, and mounted in balsam. Some blocks were embedded in celloidin.

In the frozen sections it was noted that black-stained degenerating material showed up far more distinctly in the uncleared preparations than in those which were cleared. This was due partly to the tendency of some of the Marchi material to dissolve out into the clearing reagents and partly to the extreme paleness of the background. For topographical purposes the uncleared preparations

* In receipt of a personal grant from the Medical Research Council.



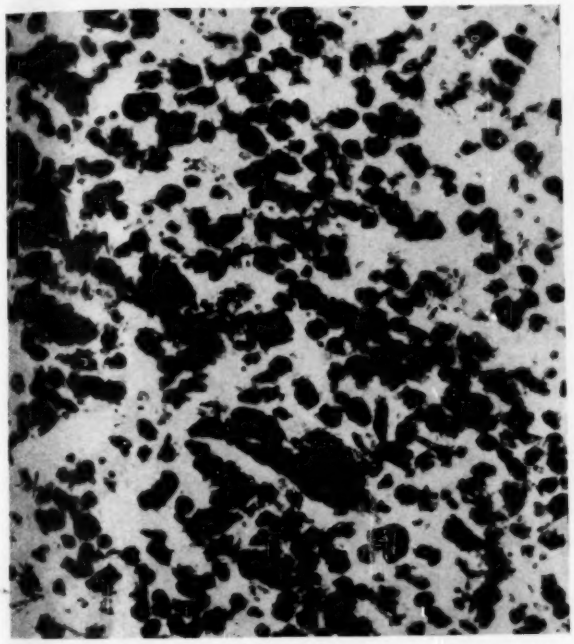


FIG. 1.—A and B.—Case A. Period of survival: nine months. Period of formalin fixation: 22 months.

FIG. 3.—Case C. Period of survival: 15 months. Period of formalin fixation: 43 months.

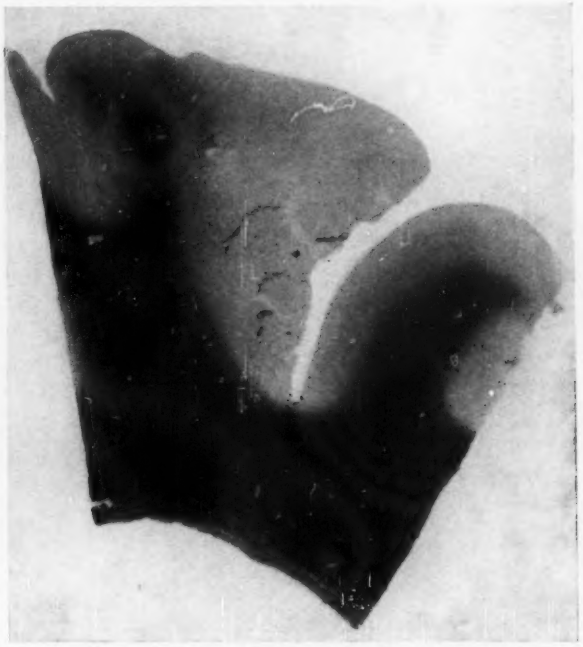


FIG. 4.—Case D. Period of survival: 12 months. Period of formalin fixation: 100 months.

FIG. 2.—Case B. Period of survival: 11 months. Period of formalin fixation: 26 months.

In all cases the photographs are from uncleared preparations. The products of degenerating myelin are stained black in every case.

were found to be completely satisfactory. When first mounted the background in these uncleared preparations was pale, in the course of the following four weeks the background darkened, and the preparations were then found to be more suitable for photography. Photographs of frozen, uncleared preparations from each of the cases are shown in Figs. 1 to 4. In no case were there any artefacts or non-penetration of the blocks. In the celloidin sections, the normal myelin became brown after the sections were in alcohol. There was, therefore, a more clearly defined background to the black-stained degenerating myelin. But as some of the black Marchi-stained material dissolved out during the process of dehydration and embedding, a less dramatic picture was obtained in celloidin than in the uncleared frozen sections.

In all four cases the Marchi-stained material was mostly contained in compound granular corpuscles. The distribution of these cells was in keeping with the distribution of demyelinated areas in sections from adjacent blocks of tissue stained to demonstrate the myelin, although the picture of myelin damage was much more striking in the Marchi preparations.

It has therefore been shown that the Marchi method is of value in demonstrating degeneration, even after prolonged storage of the tissue in formol-saline.

In work on human neuro-anatomy, comparatively little material becomes available in which conditions for tracing degenerating fibres are optimum, and frequently material has been long in formol-saline before there is an opportunity for examining it histologically. As the Marchi method allows of the demonstration of even a few degenerating fibres by staining these fibres themselves, it is of great use in determining the course of tracts or in proving the presence of fibre degeneration. It is therefore hoped that our observation that the method is applicable to long-stored material may prove of value to other workers.

Summary

Clear, positive Marchi staining is reported in four cases of head injury occurring nine to 15 months before death. Formalin fixation in these cases had been continued from nearly two years to over eight years before the material was examined by the Marchi method.

References

Bertrand, I. (1930). *Techniques Histologiques de Neuropathologie.* Masson, Paris.
Glees, P. (1943). *Brain*, **66**, 229.
Mettler, F. A., and Hanada, R. E. (1942). *Stain Tech.*, **17**, 111.
Poirier, L. J., Ayotte, R. A., and Gauthier, C. (1954). *Ibid.*, **29**, 71.
Swank, R. L., and Davenport, H. A. (1934). *Ibid.*, **9**, 129.

BOOK REVIEWS

Endokrinologische Psychiatrie. By M. Bleuler ; with a contribution by R. Hess. (Pp. 498 ; 30 figures. DM. 46.50.) Stuttgart : Georg Thieme Verlag. 1954.

Since Professor Bleuler succeeded to the Chair which his father had made illustrious he has concerned himself particularly with the clinical study of relations between endocrine disorders and mental illness. His enormous industry has enabled him to work through the large, prolix, and contradictory literature of the subject, with results evident in this useful reference book. The bibliography contains no fewer than 2,717 items, and there is good evidence that Professor Bleuler has read them all. In the general section he examines the evidence for linking specific endocrine changes to individual mental illnesses, and finds it entirely insufficient. He describes a general " endocrine psycho-syndrome " and believes that there is much similarity between it and the post-leucotomy syndrome. The psychopathology of endocrine disorders receives systematic treatment in a series of chapters occupying approximately half the book : here the investigations carried out by the author and his colleagues in Zurich serve him in good stead. The final section of the book is devoted to the endocrinology of mental disorders, especially of the schizophrenic group : it is a conscientious but rather uncritical review of a highly technical literature, for evaluating which it might be profitable in succeeding editions to enlist the cooperation of a biochemically expert endocrinologist, in the same way as Dr. R. Hess has been entrusted with the electroencephalographic contributions. It is certainly to be hoped that further editions will be forthcoming of a work so timely and serviceable.

Neurochemistry : The Chemical Dynamics of Brain and Nerve. Edited by K. A. C. Elliott, Irvine H. Page, and J. H. Quastel. (Pp. xii + 900 ; illustrated. 140*s*.) Springfield, Illinois : Charles C. Thomas ; Oxford : Blackwell Scientific Publications. 1955.

This volume brings together some 32 contributions on the chemistry of the nervous system by authors who have done original work in the field they discuss. Thus, Sir Rudolph Peters writes on pyruvate metabolism, J. H. Quastel on acetylcholine synthesis and narcosis, and D. Nachmansohn on metabolism and function in the nerve cell. Keynes and Lewis review recent work on electrolysis and nerve function, and J. D. Rossiter discusses demyelinization. In such a work there is bound to be some repetition of information, but for the clinical neurologist the book will be a valuable source of reference, since it brings together much otherwise scattered material, most of it already familiar to the biochemist in the original papers. A final brief chapter on " The Thermodynamics of the Message " by Norbert Wiener is presumably a pious offering to the cybernetic climate of opinion that was fashionable some years ago when the book was originally planned. Indeed, the references in several sections also illustrate the delay in publication that the editors mention. Nevertheless, its claim to be " a fair guide to present knowledge " seems justified. Its price will unfortunately severely restrict its sale in this country.

The Mental Hospital. A Study of Institutional Participation in Psychiatric Illness and Treatment. By Alfred H. Stanton and Morris S. Schwartz. (Pp. xx + 492 ; 5 figures, 31 tables. 35*s*. ; $ 7.50.) London : Tavistock Publications ; New York : Basic Books, Inc. 1954.

To English readers the title of this book is misleading. The co-authors, a psychiatrist and a sociologist, have described the functions and social structure of one ward in an American private institution for mental illnesses, namely the well-known Chestnut Lodge Sanitarium. This hospital employs 165 people to look after 60 patients, most of them schizophrenics, who pay a minimum of 1,500 dollars a month ; the intra-mural creed is psychoanalytical and is strong enough to replace the physical treatments of schizophrenia with a form of intensive psychotherapy. Any resemblance to an English " mental hospital " is therefore almost coincidental.

The book's sub-title is more acceptable. On their basic assumption that " at least some aspects of the disturbances of the patients are a part of the function of the institution ", Stanton and Schwartz have undertaken to survey a whole community. Nothing is sacred : the personnel (staff and patients), their morale, their modes of communication, the hierarchy of power, are all examined by the method of two years' " formal and informal participation in the life of the community ". The resulting " 9,000 single-spaced typed pages and about 3,000 pages of statistical data " are compressed into a book of nearly 500 pages.

The essence of the study is descriptive and its principal interest lies in the authors' examples of clinical and administrative practice, in their anecdotes, and in those of their speculations which derive from prolonged and intimate observation. It is to their credit that most of the field-work can be studied without reference to the more controversial body of theory which has inspired it. Though the findings do not lend themselves to valid generalization, few members of the medical profession concerned with the institutional care of the mentally sick will be able to read this study without profit and a prick of self-criticism.

The Hospitalization of Mental Patients. A Survey of Existing Legislation. Offprint from Vol. 6, No. 1, of the International Digest of Health Legislation (Pp. 100. 6*s*. 9*d*.) Geneva : World Health Organization ; London : H.M. Stationery Office. 1955.

This is a survey of the legislation regarding the admission of mental patients to hospital in more than 30 countries. The various methods of admission in different countries are surveyed under a number of heads : voluntary admission, involuntary admission, urgency admission, and admission for observation. Special categories of patients are then discussed : alcoholics and addicts, offenders and prisoners, and sexual offenders. This section of the book is perhaps the most interesting and illustrates how in many ways this country lags behind in much-needed reforms.

The Work of the Mental Nurse. (Pp. x + 154. 10*s*.) Manchester : Manchester University Press. 1955.

This survey is an analysis of the work of nursing staff in a mental hosiptal and two mental deficiency hospitals. It was directed by Mr. H. A. Goddard who analysed the work of nurses in general hospitals (published as *The Work of Nurses in Hospital Wards*, in 1955) and organized along the same lines. The purpose of the study was to determine how to make the best use of available resources. The present grave shortage of mental nursing staff makes this imperative and Mr. Goddard makes some valuable recommendations.

Psychotherapeutic Intervention in Schizophrenia. By Lewis B. Hill. (Pp. viii + 216. 37*s*. 6*d*.) London : Cambridge University Press. 1955.

This book approaches the treatment of schizophrenia from the psychoanalytical viewpoint and claims to be a " comprehensive, lucid discussion of the whole subject of treatable schizophrenia ". However, only scant mention is made of physical methods of treatment.

The author's opinion is that deep psychotherapy is the treatment of choice. He does not attempt to give any evidence to support this opinion, nor is there evidence for his many other views, for example, that the patient's " schizophrenic problems and preoccupations, interests and attitudes, derive their peculiarity primarily from his attitudes towards his mother ", a mother who is described as " immature and obsessive and hysteric " and " anxious, guilt-ridden, ashamed ".

If the author had given facts to support his views, this book might have had considerable value.

An Introduction to Psychiatry. By Max Valentine. (Pp. viii + 15 sections + appendix and index. 15*s*.) Edinburgh and London : E. & S. Livingstone. 1955.

In this book, the author's aim has been to provide " a fairly concise background of factual information " regarding psychiatry. So far as the clinical aspects are concerned, he has succeeded : psychiatric syndromes are clearly described and there is an appendix of case histories. These include verbatim interviews which give the histories a liveliness usually absent in such books.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Suicide in London. By Peter Sainsbury. (Pp. 116. 15*s*.) London : Chapman & Hall. 1955.

Gli Sviluppi Psicopatici. By C. Catalano Nobili and Giannetto Cerquetelli. (Pp. 100. No price given.) Rome : Dott. G. Abuzzini. 1955.

Auge und Zwischenhirn. By H. Becher, E. Frey, G. Leopold-Messer, J. Rohen, D. Eichner, F. Hollwich, K. Mrodzinsky, and R. Thiel. (Pp. vii + 209 ; 125 figures. DM. 19.60.) Stuttgart : Ferdinand Enke. 1955.

James Parkinson 1755–1824. Edited by Macdonald Critchley. (Pp. xvi + 268. 15*s*.) London : Macmillan. 1955.

Neural Control of the Pituitary Gland. By G. W. Harris. (Pp. xi + 298 ; 53 figures. 30*s*.) London : Edward Arnold. 1955.

Diseases of the Nervous System. Fifth edition. By Sir Russell Brain. (Pp. xviii + 996 ; 90 figures. 55*s*.) London : Oxford University Press (Geoffrey Cumberlege). 1955.

Balance Muscular. By Jacques Hindermeyer. (Pp. xviii + 130 ; illustrated. 85 ptas.) Barcelona : Editorial Noguer, S.A. 1955.

Child Psychology. By Edna Balint. (Pp. 24. 2*s*. 6*d*.) London : Cambridge University Press. 1956.

Formen des Posttraumatischen Kopfschmerzes. By Elmar E. Bues. (Pp. xii + 111 ; 28 figures. DM. 9.60.) Stuttgart : Georg Thieme Verlag. 1956.

Grosse Nerven Aerzte. Edited by Kurt Kolle. (Pp. viii + 284 ; 21 figures. DM. 29.40.) Stuttgart : Georg Thieme Verlag. 1956.

Les Grandes Activités du Lobe Temporal. Published under the direction of Pr. Th. Alajouanine with the collaboration of various authors. (Pp. 298 ; 94 figures. F. fr. 2,200.–.) Paris : Masson 1955.

Les Traumatismes Cranio-Cérébraux Fermés Récents. By MM. L. Mansuy and J. Lecuire. (Pp. 122 ; 28 figures. F. fr. 960.–.) Paris : Masson. 1955.

Les Thromboses de la Carotide Interne et de ses Branches. By MM. J. Paillas and L. Christophe. (Pp. 108 ; 25 figures. F. fr. 960.–.) Paris : Masson. 1955.

Conceptions of Modern Psychiatry. Second edition. By Harry Stack Sullivan. (Pp. xiii + 298. 32*s*. 6*d*.) London : Tavistock Publications, Ltd. 1955.

The Interpersonal Theory of Psychiatry. By Harry Stack Sullivan. (Pp. xviii + 393. 35*s*.) London : Tavistock Publications, Ltd. 1955.

J.–M. Charcot, 1825–1893 : Sa Vie—Son Oeuvre. By Georges Guillain. (Pp. 188 ; 9 figures. F. fr. 1,400.–.) Paris : Masson. 1955.

Le Système Nerveux Périphérique. By Guy Lazorthes. (Pp. 348 ; 214 figures. F. fr. 4,200.–.) Paris : Masson. 1955.

Contributi del Laboratorio di Psicologia, Vols. xlviii and xlix. (Pp. 426 and 540 respectively ; illustrated. No price given). Published by Vita E Pensiero, Milan. 1955.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 67.

OBSERVATIONS ON THE EXTENDED USE OF THE MARCHI METHOD

BY

MARION C. SMITH

From the National Hospital for Nervous Diseases, Queen Square, London

It has previously been reported (Smith, 1951) that the Marchi method applied to human material is useful in demonstrating degeneration in nerve fibres even when the interval between the occurrence of the lesion and death exceeded one year. Also (Smith, Strich, and Sharp, 1956) the Marchi method can be applied when the material has been stored in formol-saline for as long as eight years. This latter observation is contrary to traditional opinion; it is important because it points to the possible use of the Marchi method on material that would previously have been considered totally unsuitable for this technique. The purpose of this paper is to report an investigation of the effects of storage in formol-saline on degenerating nerve fibres in human material, and to draw attention to the relation between the stage of degeneration and the kind of Marchi staining obtained.

The spinal cords from 18 patients were examined. Each patient had had a cordotomy at a known interval before death. In every case Marchi preparations were made after 10 to 14 days' fixation. During the next 15 to 72 months spare blocks of material were stored in 10% or 20% formol-saline. Slices were then cut from the blocks and a second series of Marchi preparations was made. The most satisfactory of these later preparations were found to be uncleared frozen sections prepared by the Swank-Davenport-Glees technique (Glees, 1943) but mounted directly after cutting in glycerine jelly (Smith and others, 1956); frozen sections cleared in cedar-wood oil and mounted in Canada balsam, and celloidin sections, some counterstained, were also prepared.

Relationship between Period of Survival and Period of Fixation

In every case the sections prepared after the short period of fixation contained black-staining, Marchi-positive material. In the sections prepared after prolonged storage in formalin, on the other hand, black-stained, Marchi-positive material was present in some of the cases only, and there proved to be a correlation between the period of survival after a lesion and the occurrence of Marchi-positive material. After prolonged fixation it became evident that when the period of survival between the lesion and death was 75 days or less, Marchi-positive material was absent or present in only negligible amounts. When, however, the period of survival exceeded 75 days Marchi-positive staining material was present in every case. The amount of the Marchi-positive material in these cases varied in direct relation to the length of the period of survival after the lesion: thus in the cases with survival periods of 81 to 112 days there was much less material than in the cases with longer survival periods. The most vivid picture was obtained in the cases with survival periods of 390 and 466 days (Cases 55 and 56). This correlation between the length of the period of survival and the absence or presence of Marchi-positive material in sections prepared after prolonged storage in formol-saline is summarized in the Table.

Photographs from representative cases are shown on Page 69. In each case, photographs are given from the series of sections prepared after 14 days'

TABLE

FROZEN MARCHI PREPARATIONS MADE AFTER PROLONGED STORAGE OF TISSUE IN FORMOL-SALINE

Case Number	Period of Survival after Cordotomy (days)	Period in Formol-Saline (months)	Black-staining Marchi-positive Material
31	23	37	(±)
7	24	63	−
33	39	35	−
34	53	33	−
2	75	66	−
37	81	15	+
38	87	24	+
47	101	22	+
32	101 (after left operation)	31	+
20	110	60	+
35	112	64	+
10	141	72	+
22	154	65	+
21	159	70	+
32	172 (after right operation)	31	+
3	205	66	+
11	239	42	+
55	390	43	++
56	466	20	++

fixation (A) and from the series prepared after prolonged periods of fixation (B). The two series have been taken from the same region of the cord so that comparison of the areas of degeneration in the two sections in each case is justified.

In Case 34, Fig. 1 (period of survival, 53 days), the section prepared after 14 days' fixation (A) contains numerous black-stained bodies, indicating degeneration of nerve fibres, but in the section prepared after 33 months' fixation (B) there is no black staining, and therefore, in Marchi preparations, no evidence of any degeneration of nerve fibres.

In Case 37, Fig. 2 (period of survival, 81 days), there is abundant black-stained material in the section prepared after 14 days' fixation (A). In the section prepared after 15 months' fixation (B), there is a little black-stained material in the region of the most intense staining in the section prepared after short fixation.

In Case 47, Fig. 3 (period of survival, 101 days), black-stained material is present both in the section after 14 days' fixation (A) and that after 22 months' fixation (B), but it is rather more intensely stained in the section prepared after 14 days' fixation.

In Case 55, Fig. 4 (period of survival, 390 days), abundant black-stained material is present in the sections, both after 14 days' fixation (A) and after 43 months' fixation (B). The intensity of the staining is about the same in the two sections.

In the other cases in Table 1, the findings were similar to those shown here. Within the limits of the material examined, the longer the period of survival after the lesion, the more vivid is the black zone of degeneration in the sections prepared after prolonged fixation.

When a lesion occurs three to 10 weeks before death, the period of fixation in formol-saline must be short for the satisfactory demonstration of degenerating myelinated fibres by the Marchi method; when the lesion occurs 10 weeks to 15 months before death, the period of fixation in formol-saline can be short or long. Most of the Marchi-positive material is not demonstrable in tissue kept in formol-saline for 30 months (or possibly less) when the lesion occurred three to 10 weeks before death. When the time between the lesion and death is an intermediate period, about 10 to 16 weeks, the degeneration is more clearly shown up when the period of fixation in formol-saline is short. When the time between the lesion and death is six months or longer the degeneration is as clearly shown up after long as after short periods of fixation.

Extracellular and Intracellular Marchi-positive Material

These conclusions lead one to ask the question: What changes occur in the black-staining material during the various periods of survival, so that it reacts differently to short and to long periods of storage in formol-saline? A histological answer to this question will now be given. When the black-stained material is examined under higher magnification, certain differences are seen between the material from cases with short survival periods and that from cases with long survival periods.

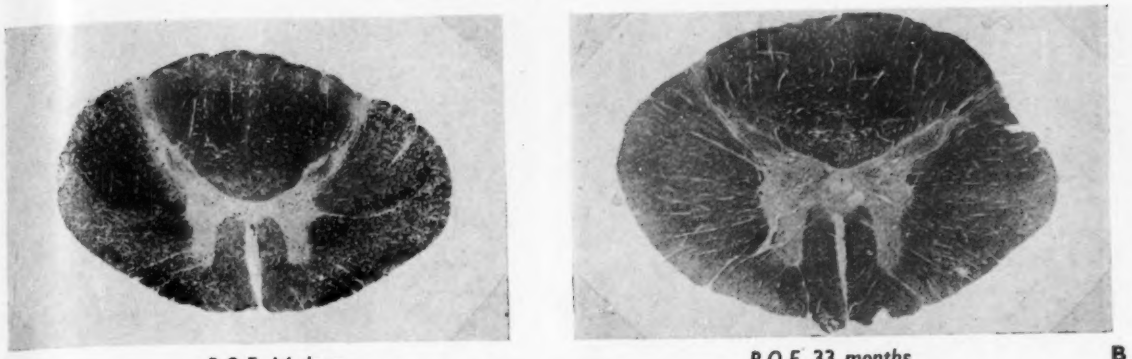
On pages 70 and 71 are photographs which are magnified views from those on page 69 (the area magnified is shown in the small diagrams). On pages 70 and 71, as on page 69, the (A) figures are from the sections prepared after 14 days' fixation, and the (B) figures are from those prepared after prolonged periods of fixation. In addition to the figures derived from those on page 69, there are two extra figures: Fig. 5A′ is a photograph of a longitudinal section from Case 34, prepared after 14 days' fixation, and Fig. 8B′ is a frozen section from Case 55 prepared after 43 months' fixation and dehydrated and cleared before mounting.

In Case 34, shown in Fig. 5A, A′ and B, the period of survival was 53 days.

In Figs. 5A and A′ the black-stained material consists of swollen and disrupting myelin sheaths breaking up into globules. No scavenger cells containing black globules can be seen. This is the classical picture of degenerating nerve fibres as demonstrated by the Marchi method. In Fig. 5B, which is a comparable section made after prolonged fixation in formol-saline, there is almost no black staining to be seen. All the other cases in the group surviving 21 to 75 days present a similar picture; very little black staining, or none at all, was found after prolonged fixation.

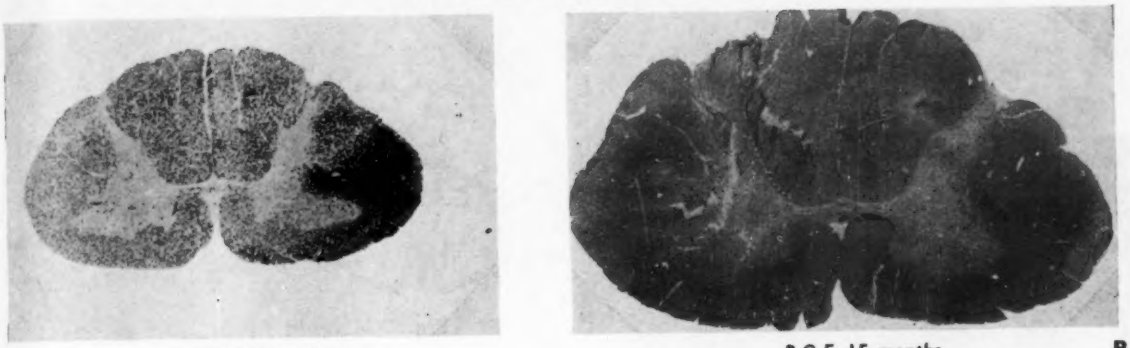
In Case 37, shown in Figs. 6A and B, the period of survival was 81 days. In Fig. 6A there is more abundant degeneration than in Fig. 5A, but the pattern of numerous rounded bodies of different sizes is comparable in the two cases. The bulk of the black staining material appears to be extracellular. In Fig. 6B there are some black-stained bodies, but these are very few compared with the number stained in the section prepared after 14 days' fixation. There are also areas of indefinite, greyish, rather "granular" staining in the background.

In Case 47, shown in Figs. 7A and B, the period of survival was 101 days. There is abundant staining in the preparations after short periods of fixation



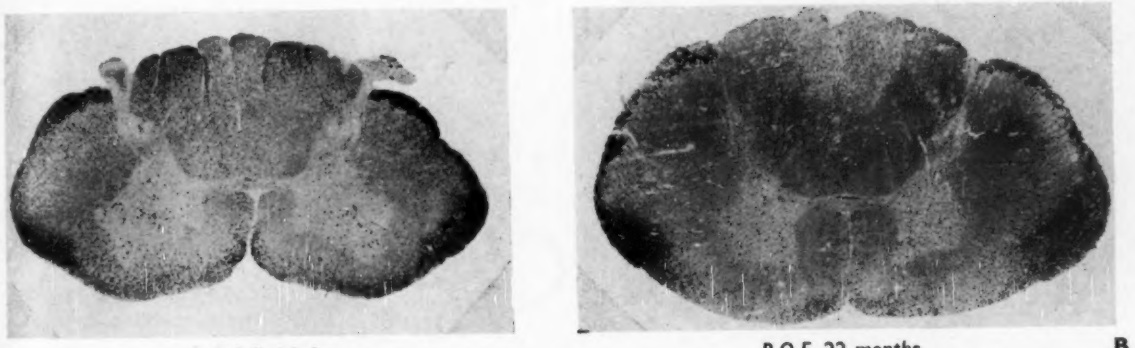
A P.O.F. 14 days P.O.F. 33 months B

Fig. 1.—Case 34 : P.O.S. 53 days



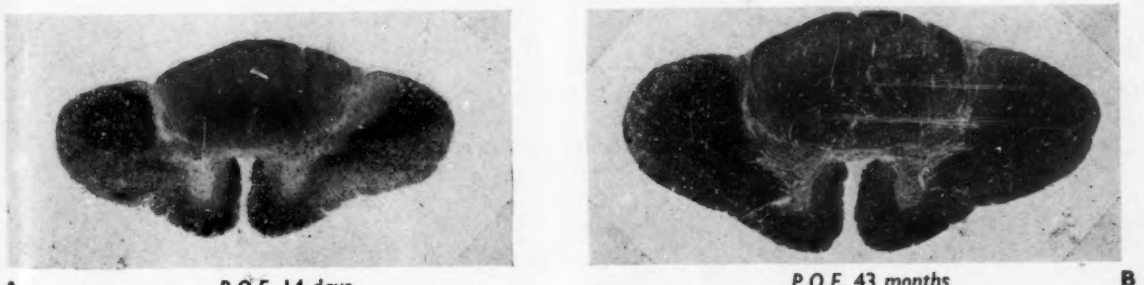
A P.O.F. 14 days P.O.F. 15 months B

Fig. 2.—Case 37 : P.O.S. 81 days



A P.O.F. 14 days P.O.F. 22 months B

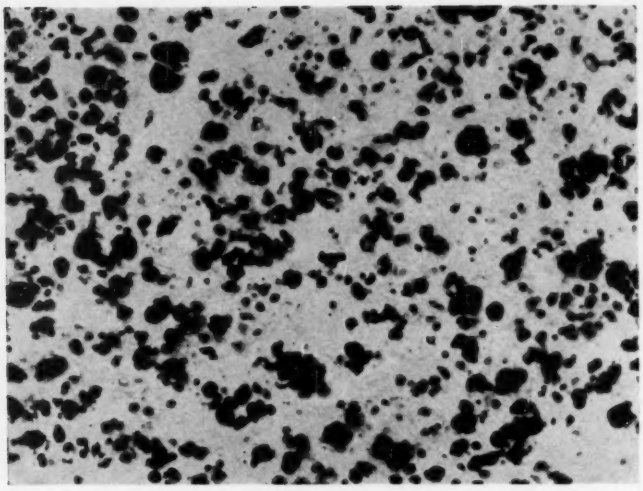
Fig. 3.—Case 47 : P.O.S. 101 days



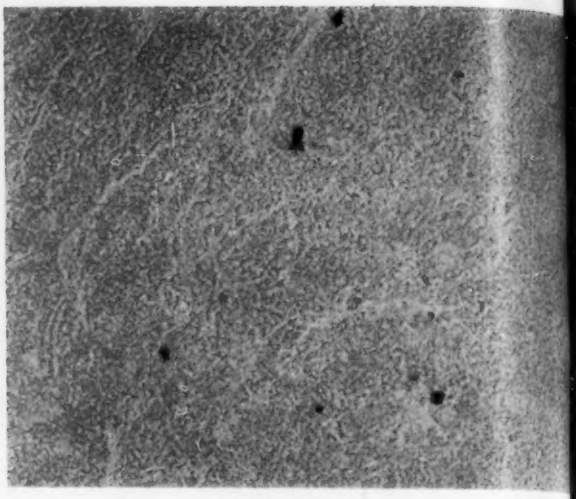
A P.O.F. 14 days P.O.F. 43 months B

Fig. 4.—Case 55 : P.O.S. 390 days

P.O.S. = period of survival ; P.O.F. = period of fixation.



A



A′

A : *P.O.F. 14 days*

A′ : *P.O.F. 14 days* (longitudinal section)

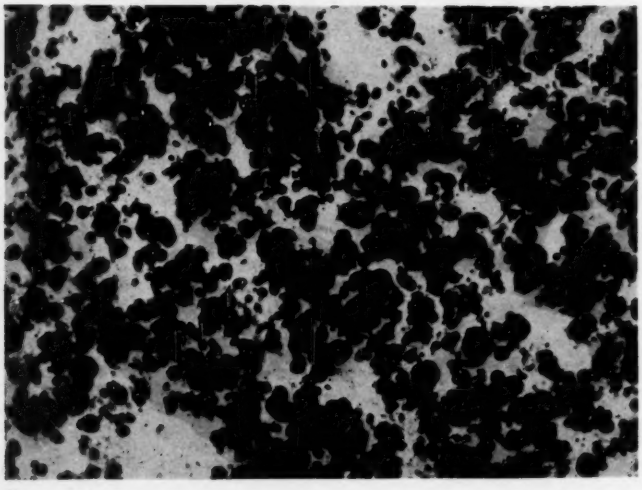
B : *P.O.F. 33 months*

Fig. 5.—Case 34 : P.O.S. 53 days

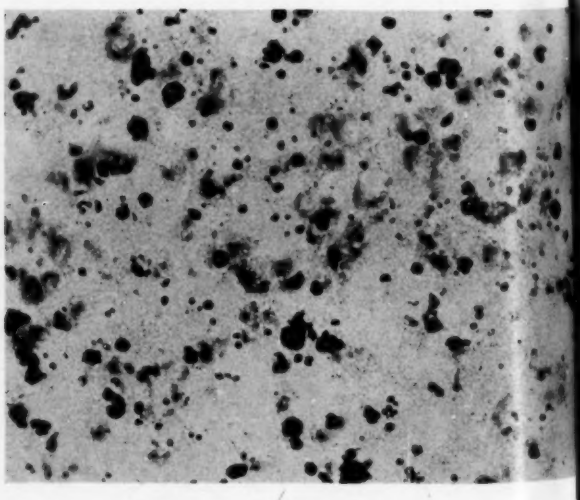
Fig. 6.—Case 37 : P.O.S. 81 days

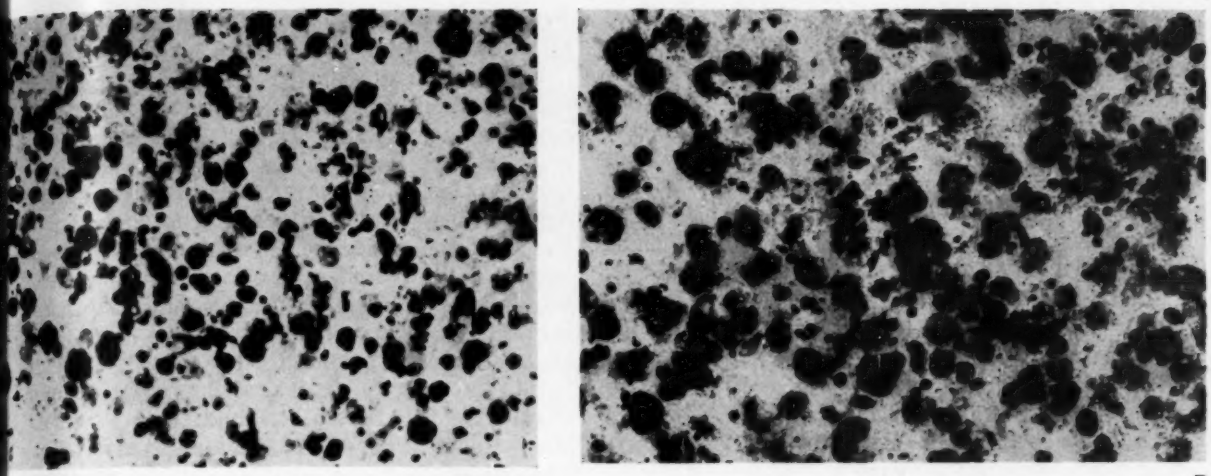
A : *P.O.F. 14 days*

B : *P.O.F. 15 months*



A

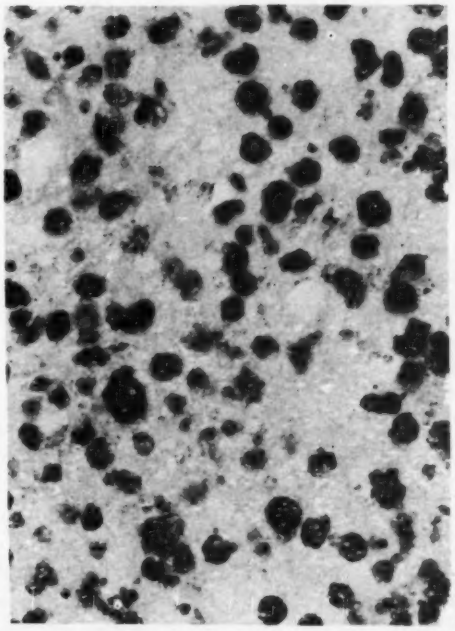




B

A : *P.O.F. 14 days*
B : *P.O.F. 22 months*

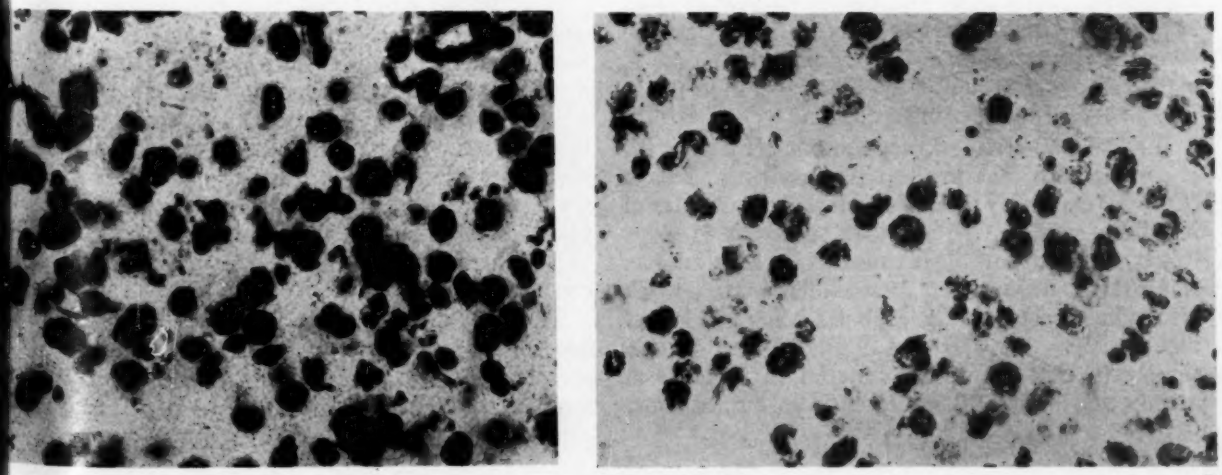
Fig. 7.—Case 47 : P.O.S. 101 days



A

Fig. 8.—Case 55 : P.O.S. 390 days

A : *P.O.F. 14 days*
B : *P.O.F. 43 months*
B′ : *P.O.F. 43 months*
(cleared section)



B′

and also after prolonged fixation. In Fig. 7A there are numerous black bodies similar to those seen in Figs. 5A and 6A, and many of these do not appear to be contained in cells; there are also numerous "groups" of greyish "globules" which do not seem to be lying free but to be contained within cells. In Fig. 7B there are large regular black bodies, some smaller black bodies, and many groups of small black or grey "globules." In some of these groups there is also a larger black body.

In Case 55, shown in Figs. 8A, B, and B′, the period of survival was 390 days. In Fig. 8A the appearance of the black-stained material is much more regular than in the other three cases. There are few, if any, extracellular black-staining bodies of varying size, as are present in the other cases. The black material appears to be entirely intracellular, and to be in small "globules". Some of the cells contain globules which stain a greyish colour, others are intensely black. In the uncleared section prepared after prolonged fixation, the black material is in the form of rather regular homogeneous looking, black masses; in the cleared preparation, B′, a picture comparable to 7A is obtained. It is evident that the black and grey globules are contained in cells, which must be compound granular corpuscles. The homogeneous masses in the uncleared preparation, Fig. 8B, are obviously the same intracellular material seen in Fig. 8B′. The preparations made after short and after prolonged periods of survival are more comparable in this case than in the cases with shorter survival periods. If Fig. 6B is now re-examined, it can be seen that the groups of greyish material resemble the intracellular material in Figs. 7B and 8B and B′. It seems likely that they are scavenger cells in this case also.

If all the (A) preparations are now re-examined, it can be seen that in the cases with periods of survival of 53 to 81 days, little, if any, of the black material is intracellular and that most of it lies free in the tissue. In the case surviving 101 days (Case 47) some of the material is intracellular and some is extracellular. In the case surviving 390 days (Case 55), all the material is intracellular.

If all the (B) series of preparations are examined, it can be seen that in the case surviving 53 days (Case 34) extremely little of the degenerated material has been stained. In the case surviving 81 days (Case 37), part of the extracellular material has stained. A little of the intracellular material has also stained, some of the globules being black and others grey. Fig. 7B and Figs. 8B and B′ are similar in that the black material in Fig. 7B is mainly, and in Figs. 8B and B′ entirely, intracellular.

From these cases and the other cases in the series certain conclusions can be drawn.

It is apparent that the Marchi method stains black certain degeneration products of myelin, whether the material is situated extracellularly amongst the nerve fibres or intracellularly in scavenger cells. The appearance of the products of degenerating fibres is dependent not only on the length of the period of survival, but also on the length of the period of fixation. The amount of extracellular material which is stained black is greatest when the period of fixation is short. With longer periods of fixation there is a gradual diminution in the amount of extracellular material demonstrable by the Marchi method, and eventually, after prolonged periods of fixation, no extracellular material at all can be demonstrated. It appears to be probable that the longer the period of survival, the longer can the tissue be stored in formol-saline and some extracellular material still be demonstrated. The exact lengths of time during which cases with periods of survival of less than 80 days can be stored in formol-saline and extracellular material still be stained has to be determined. With respect to the intracellular material, much of it is stained however long the tissue has been preserved in formol-saline. Although to a markedly less extent than with the extracellular material, it appears to be likely that there is some correlation between the length of the period of survival and the amount of intracellular material still demonstrable after prolonged fixation. The longer the period of survival, within certain limits, the longer can material be stored in formol-saline, and as much intracellular Marchi-positive material as was stained after short periods of fixation still be demonstrated. But it must be stressed that prolonged periods of fixation do not alter the positive Marchi picture to anything like the same extent when the material is in the intracellular stage as when it is in the extracellular stage.

It is to be noted that the distribution of the degenerating fibres indicated by black staining in the Marchi preparations corresponds exactly to the distribution indicated by other staining methods, whether the period of survival was short or long. It can then be concluded that the black-staining material remains in approximately its original site, even when the period of survival is more than a year. This applies to the intracellular material as well as to the material lying free between the fibre mesh.

This finding, that the material derived from degenerating myelin remains *in situ* for at least 15 months, is surprising; for it might have been thought that once the material had been taken up

by scavenger cells it would have been removed from the site of degeneration and have entered the blood stream. As this intracellular black-staining material remains *in situ*, the Marchi method is still useful in tracing degeneration when the period between the lesion and death is such that these products of myelin degeneration, which stain black, are all taken up by scavenger cells.

The amount of intracellular black-staining material is of course related to the amount originally available from the myelinated nerve fibres; it follows that where a tract consists of thinly myelinated fibres the Marchi method applied after prolonged fixation will not give good staining, any more than it does in the early stages of fixation.

Estimation of Period of Degeneration by the Marchi Method

In all the cases described here, the lesion which caused degeneration in the nerve fibres was a surgical one, consisting of actual transection of the fibres; the exact period of survival after the lesion was known. From these cases, the appearances of degeneration at the various intervals between the lesion and the death of the patient, as shown by the Marchi method, can be seen. Thus a series such as these cases with lesions made at known intervals between 21 and 466 days before death can be used as a standard of comparison for estimating when a lesion occurred, and also whether the degeneration seen in nerve fibres occurred all at one time or if it occurred in more than one stage. It is probable that a full comparison can justifiably be made between the series of cases reported here and other cases in which the lesion is traumatic. But whether the process of degeneration in other pathological conditions is similar enough to warrant a direct comparison remains to be investigated. In such cases, even if conclusions as to the duration of the condition cannot be drawn, at least it can be concluded whether the degeneration occurred at one time, or continuously, or in stages at dispersed intervals.

In traumatic cases, when there is abundant extracellular black-staining material, and very little intracellular material, it may be concluded that the degeneration of nerve fibres has been going on for less than 75 days. When there is a moderate amount of intracellular material, staining grey in many cells, and staining black in a few cells as well as in some extracellular material, it is probable that the degeneration of nerve fibres occurred three to four months before death. If in addition to the intracellular material there are very large amounts of extracellular material, then the degeneration may be assumed to be continuous, or to have been repeated during the three to four months preceding death. When there are numerous cells containing black-staining material, only a few cells containing grey-staining material, and no extracellular material, the degeneration of the fibres may be taken as having occurred about a year before death. The presence of many grey-staining scavenger cells and/or free black-staining material would indicate more recent degeneration also.

Perhaps it should be added that this use of the Marchi method to estimate the duration of a lesion is not designed to replace other histological methods of doing this but to supplement them.

Summary

An investigation was undertaken of the application of the Marchi method to tissue stored for various periods in formol-saline. It was found that all the black-staining, Marchi-positive material resulting from degeneration of nerve fibres is at first extracellular and later intracellular. For approximately 10 weeks after a lesion the material is mainly extracellular, after this time an increasing amount of the material is intracellular, and by 12 months after the lesion the material is entirely intracellular. When it is in the extracellular state the material can be stained very clearly with the Marchi method after limited periods of fixation, but most of it does not stain when the material has been fixed for two and a half years or longer. When it is in the intracellular state much of it stains clearly after both limited and prolonged periods of fixation in formol-saline. In material in which the lesion occurred a year or longer before death, particularly vivid staining is obtained after prolonged fixation.

It is a pleasure to thank Dr. E. A. Carmichael for his help and encouragement in this investigation, Mrs. J. A. Mills and Mr. Peter Sharp for all the technical work involved, and Mr. J. A. Mills for his kindness in taking the photographs.

References

Glees, P. (1943). *Brain*, **66**, 229.
Smith, M. C. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 222.
——, Strich, S. J., and Sharp, P. (1956). *Ibid.*, **19**, 62.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 74.

THE RECOGNITION AND PREVENTION OF ARTEFACTS OF THE MARCHI METHOD

BY

MARION C. SMITH

From the National Hospital for Nervous Diseases, Queen Square, London

For more than 80 years now the Marchi method has been used for the demonstration of degenerating nerve fibres. The usefulness of this method is shown by the fact that it has stood the test of time and is still the standard method of demonstrating degenerating myelin. But the method has two main limitations : it is of use only at certain stages of the process of the degeneration and it is marred by the frequent occurrence of artefacts.

In recent papers (Smith, 1951, 1956 ; Smith, Strich, and Sharp, 1956), my colleagues and I have shown that the Marchi method is far less limited than was previously believed. For it is a useful method of demonstrating degeneration in tracts in man when there is more than a year between the occurrence of the lesion and the death of the patient. And further, it can be used with great effect when the tissue has been stored for many years in formalin.

Since the occurrence of artefacts remains a serious disadvantage of the Marchi method, the major part of this paper will describe various forms of pseudo-Marchi staining and indicate how these artefacts can be distinguished from true degeneration. In addition, some technical recommendations will be given ; these are based on considerable experience of the Marchi method in tracing degenerating fibres in the human central nervous system.

THE RECOGNITION OF PSEUDO-MARCHI ARTEFACTS

The appearance of true degeneration will first be briefly considered, and then the main forms of artefact will be described and illustrated. For descriptive purposes the terms " longitudinal section " and " transverse section " will refer solely to the long axis of the degenerating fibres.

True Degeneration

The appearance of degenerating fibres in Marchi preparations is related to the period of survival between the occurrence of the lesion and the death of the patient. When the period of survival is 20 to 80 days, most, if not all, of the black-stained material derived from the degenerating fibres is extracellular. In transverse section it is in the form of round bodies (Figs. 2, 5, and 6). In longitudinal section it is at first in the form of irregularly swollen threads (Figs. 7 A and B, Fig. 9) and later as spherical bodies, which, to some extent, are arranged in strings (Figs. 8 A and C, Fig. 10). There are also compound granular corpuscles containing numerous black globules lying among the degenerating fibres. These increase in number the longer the survival period. In cases with survival periods of about 140 days most of the black material is intracellular, and in cases with survival periods of 250 days or more there is rarely any extracellular black material (Fig. 3). In general, degenerating fibres are more easily recognized in longitudinal than in transverse section ; this applies particularly to fine fibres.

Artefacts

A constant feature of true degeneration is its continuity : the pattern of staining conforms with the known form of the structures ; the black staining indicates fibres, and thus it may be traced across a section, from one section to the next and from one block to the next. In most forms of artefact, this feature of continuity is absent ; the black staining does not form a pattern consistent with the known structure of nerve fibres. This random distribution is the most important criterion by which to judge between false and true degeneration.

Some artefacts resemble true degenerating fibres seen in transverse section, while others resemble degenerating fibres in longitudinal section. They will be considered in the following three groups, of which the first is most important in transverse sections, the second and third in longitudinal sections : (1) pseudo-Marchi dust ; (2) pseudo-Marchi

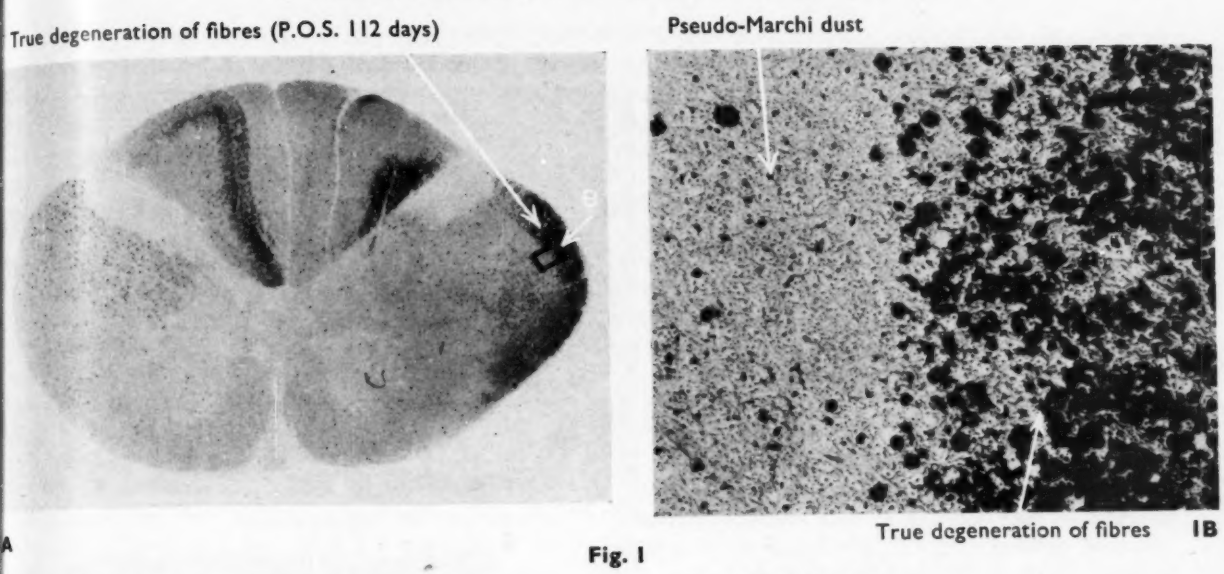


Fig. 1

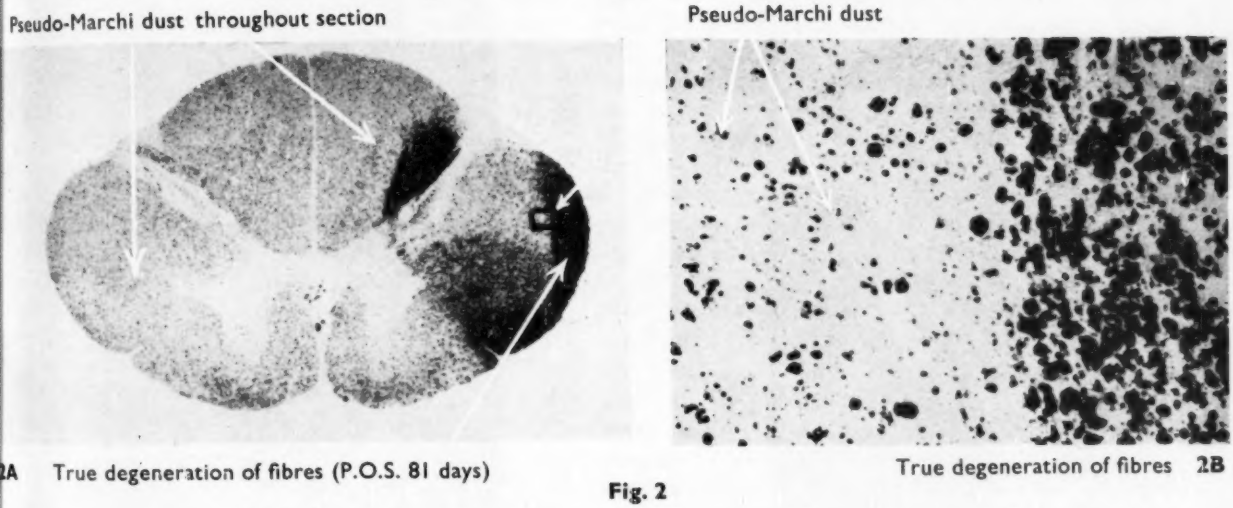

Pseudo-Marchi dust throughout section
Pseudo-Marchi dust
2A True degeneration of fibres (P.O.S. 81 days)
True degeneration of fibres 2B

Fig. 2

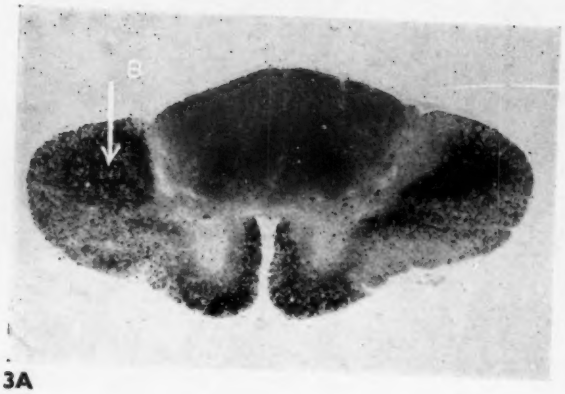
The order of presentation of the figures is governed by the occurrence of artefacts and not by the stages of nerve fibre degeneration. P.O.S. = period of survival; P.O.F. = period of fixation.

staining of normal fibres; (3) massive, localized pseudo-Marchi staining.

The terms " pseudo-Marchi staining ", " Marchi dust ", and " Marchi bodies " are used by all workers in this field. Unfortunately there has been no standardization, and so these terms need to be defined by every worker as he uses them. In this paper, the term " Marchi bodies " will be used to indicate true degeneration of fibres. All other terms indicate various forms of artefact.

(1) **Pseudo-Marchi Dust.**—Pseudo-Marchi dust occurs as fine or coarse particles or as an organized network of particles. The fine and the coarse particles constitute a common form of artefact. The dust is usually scattered throughout the whole section (Figs. 1 and 2). Sometimes, however, it is more abundant in certain tracts and may even be confined to some tracts (Fig. 4). There is no greater concentration in the area of degenerating fibres than elsewhere. The dust occurs as fine or coarser particles ranging in size from 1 μ up to about 30 μ diameter (Figs. 1, 2, 4, and 5). When this artefact occurs in the form of a fine dust it does not usually cause any difficulties in interpretation; it merely spoils the appearance of the preparation, making it dirty looking. The particles are usually too fine to be confused with Marchi bodies, and, like most other artefacts, they show a random

True degeneration of fibres
(Intracellular Marchi-positive material) (P.O.S. 390 days)



3A

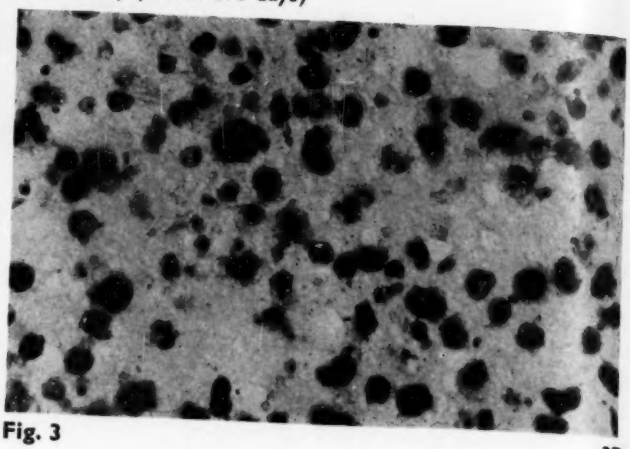


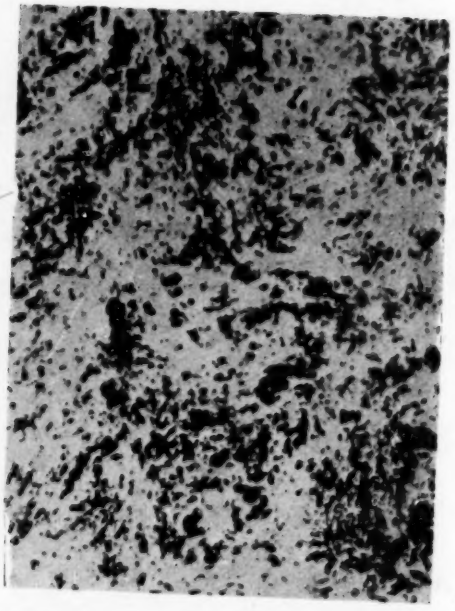
Fig. 3

3B

4A

Pseudo-Marchi dust in some normal tracts only

Abundant dust in normal tracts



4B

Little dust

4C

Fig. 4

distribution. One point of distinction from the rounded Marchi bodies of true degeneration is the angulated outlines of many of the particles (Fig. 2). Many of the larger particles seem to be formed from aggregates of the smaller particles (Figs. 4 and 5). The coarser particles tend to confuse the picture when the true degenerating fibres are all of small diameter, and also to obscure the details on the boundaries of a zone of degeneration, for they may mask the course of a few fibres as the latter leave the main mass of fibres. This is seen in Fig. 2 : there is a peppering of pseudo-Marchi dust throughout the section but the true degenerating fibres can be clearly distinguished. Only on the edge of the main mass do the pseudo-Marchi particles cause confusion. The larger black bodies are only present near the main mass of degenerating fibres, and they can be traced through successive sections. They can therefore be interpreted as degenerating fibres. The fine particles are similar in appearance and number to those scattered throughout the rest of the section, and throughout the whole cord. They cannot be traced from section to section. They are therefore interpreted as pseudo-Marchi dust, although it is possible that a few very fine degenerating fibres may also be present. But there is one further point that makes it unlikely that the fine particles are derived from degenerating fibres : this is the period of survival. In this case the patient lived 81 days after the lesion ; it is uncommon to find evidence of active degeneration in very fine fibres after such a long interval.

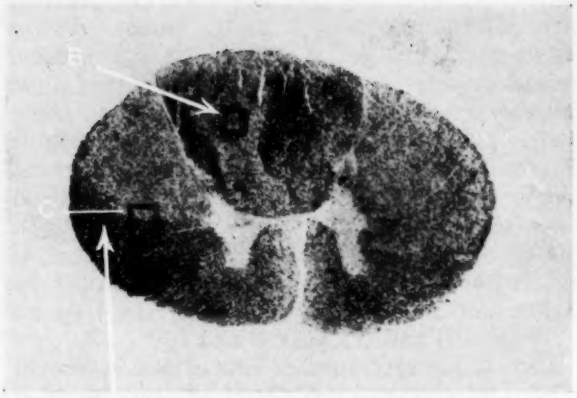
The coarse pseudo-Marchi dust particles may sometimes reach such large numbers that they obscure details of the true degenerating fibres, for the whole background of the section is then full of black-stained " bodies ". This is shown in Figs. 5 and 6. Each individual black body cannot, in such a section, be infallibly identified as either a degenerating fibre or as pseudo-Marchi dust. But information can still be gained as to the whole pattern of degenerating tracts, which by density and consistency of staining from section to section can be distinguished from the dust, which varies in distribution and amount from section to section.

As was mentioned above, pseudo-Marchi dust may also appear as an organized network. This is a form of artefact which is not easily confused with true Marchi staining, but it may completely hide the true degenerating fibres. The black " particles " form large irregular black masses. A particularly severe example of this artefact is shown in Figs. 6 B and C.

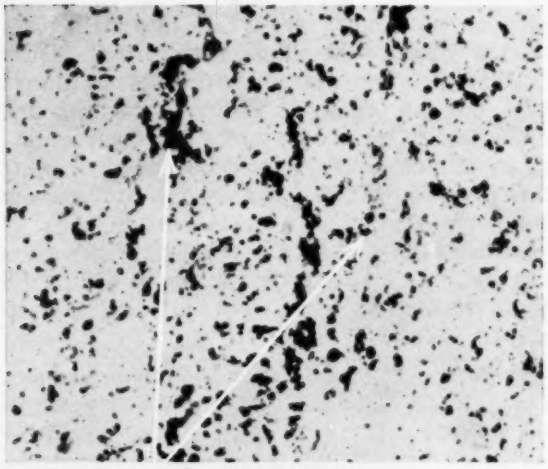
(2) **Pseudo-Marchi Staining of Normal Fibres.** —This form of artefact closely mimics the appearance of true degeneration, particularly when seen in longitudinal sections. It tends to occur in certain characteristic sites, such as the larger cranial nerves, especially the second, fifth, seventh, and eighth, and also in the corpus callosum. It seems to be associated with post-mortem damage to the tissues. Fibres which have been pulled on at necropsy become stained over a considerable length ; they then resemble fibres which were degenerating before death. They differ from true degenerating fibres in that the diameter of the fibres is constant throughout and in that lengths of the fibre remain unstained while other lengths are stained black (Figs. 8 A and C ; Fig. 11). The true degenerating fibre, it will be remembered, has a beaded or broken-up outline and stains black throughout (Figs. 7 A and B ; Figs. 8 A and B ; Figs. 9 and 10).

There is, however, another form of pseudo-Marchi staining of normal fibres. If at any time between death and fixation some droplets of myelin escape from the neurilemmal sheath they may stain black with the osmic acid solution (Fig. 11). These stained droplets have the same appearance as Marchi bodies, but can usually be distinguished from true Marchi bodies on account of their distribution : they usually occur in the neighbourhood of fibres showing pseudo-Marchi degeneration and are not particularly associated with the main mass of degenerating fibres which can be traced from section to section. This latter point serves to distinguish them in transverse sections from the true degenerating fibres.

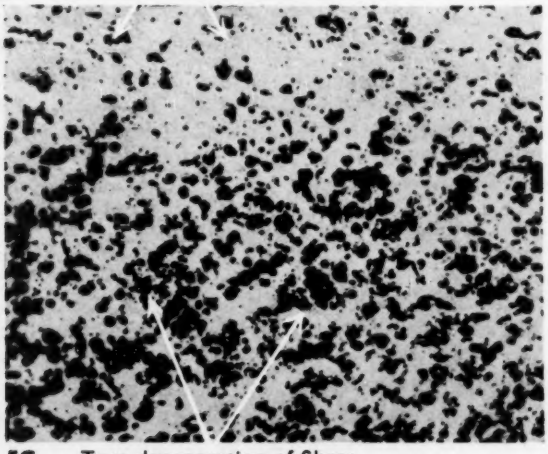
(3) **Massive, Localized Pseudo-Marchi Staining.** —Occasionally there occurs a very dense patch of black staining, with some characteristics like those described under (2), (Figs. 12 and 13). This massive black staining is particularly liable to occur deep in a large block, in an area of densely packed nerve fibres ; it may enclose an unstained zone. It is characterized by the intensity of the coal black staining, confined to one area of the block. In sections through such an area, the whole region is usually peppered with pseudo-Marchi dust. Every fibre is stained intensely black. Such a mass of intense black staining never occurs with true degenerating fibres. When the fibres are examined, the characteristics mentioned under (2) are seen—the constant diameter and patchy staining of the fibres. In this case the patchiness is demarcated at the edge of the black area, so that all the fibres within the black area are deeply stained, and their extensions beyond it are left unstained. The outlines of some of these stained fibres may be irregular, but the other features serve to distinguish them from degenerating fibres. This form of artefact differs



5A True degeneration of fibres (P.O.S. 23 days)

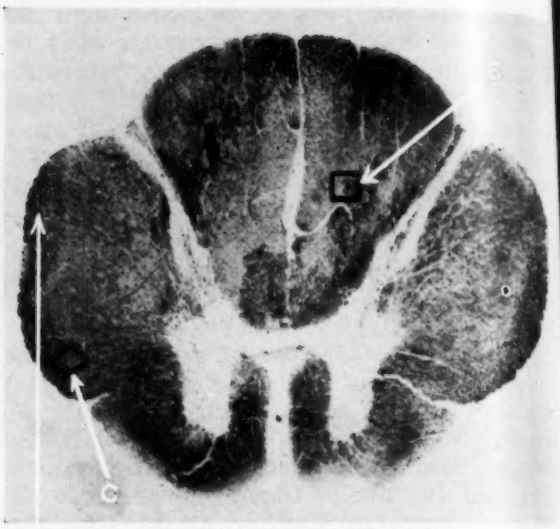


5B Coarse pseudo-Marchi dust

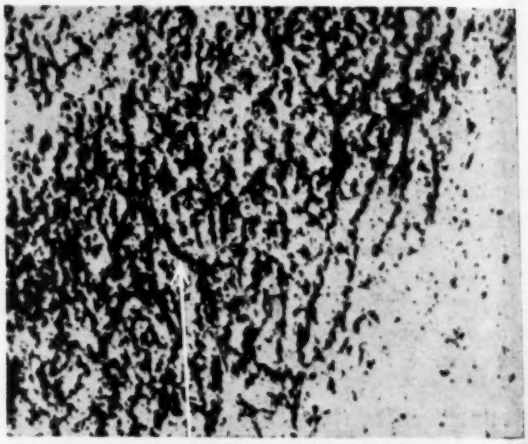


5C True degeneration of fibres

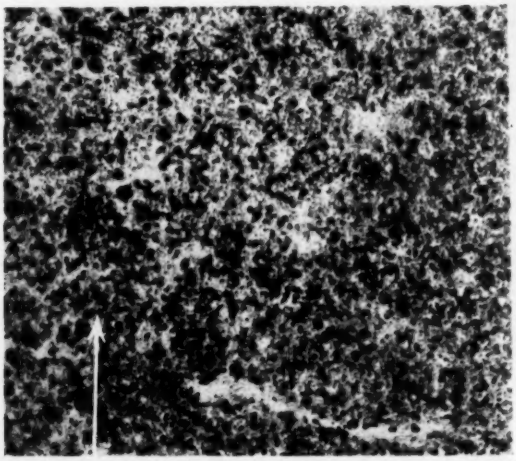
Fig. 5



True degeneration of fibres (P.O.S. 75 days) 6A



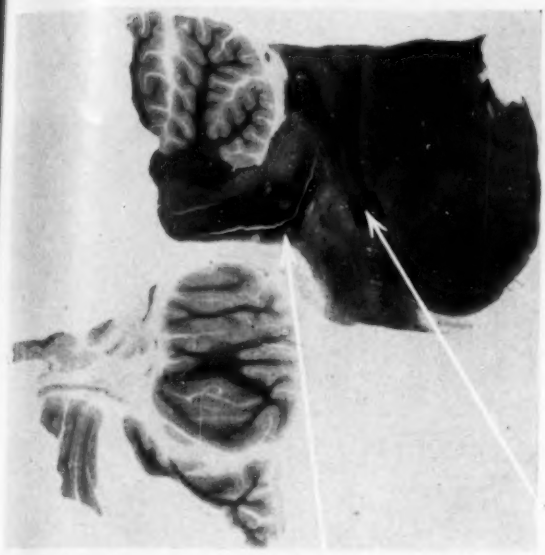
Organized network of pseudo-Marchi dust 6B



Degenerating fibres hidden by coarse pseudo-Marchi dust 6C

Fig. 6

Fine pseudo-Marchi dust



7A Area of non-penetration by osmic acid solution

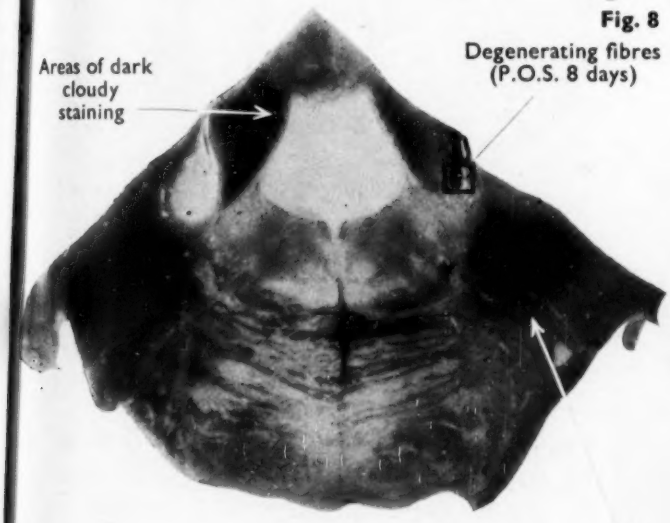
True degeneration of fibres (P.O.S. 23 days) 7B

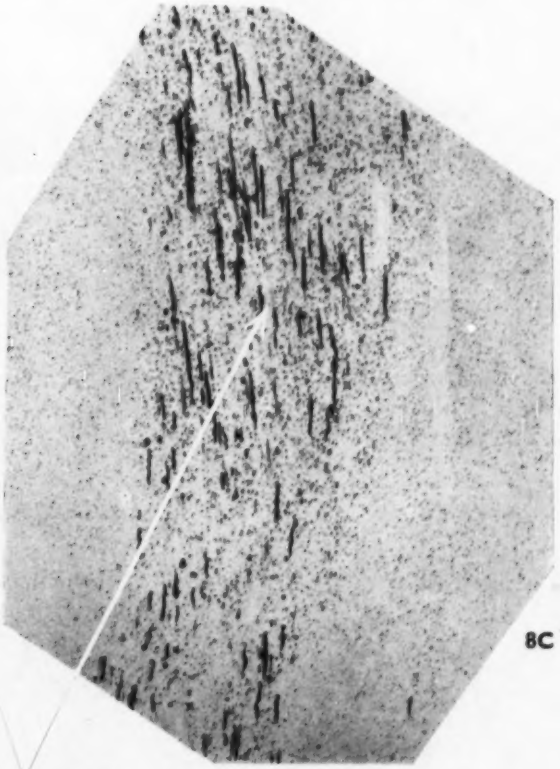
Fig. 7

Fig. 8

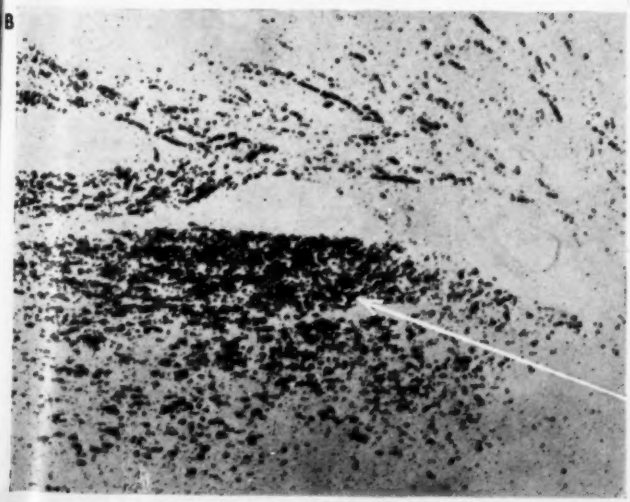
Areas of dark cloudy staining

Degenerating fibres (P.O.S. 8 days)





8C



Pseudo-Marchi staining of normal fibres

True degeneration of fibres

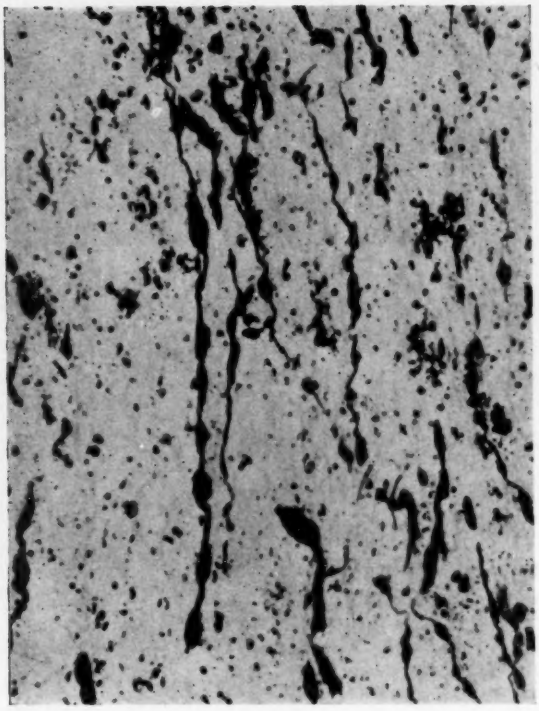


Fig. 9

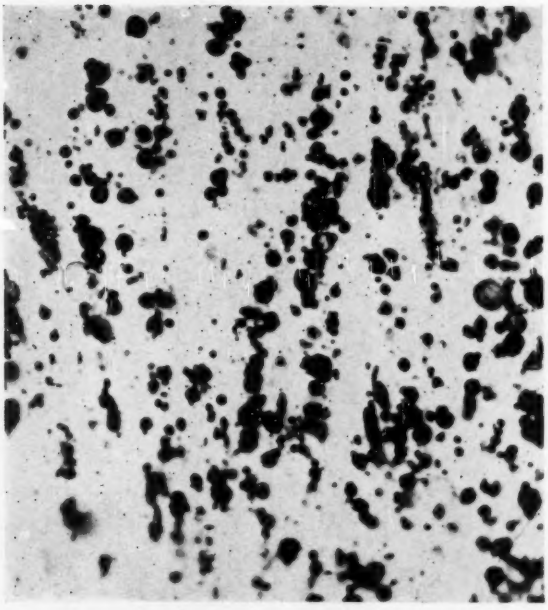


Fig. 10

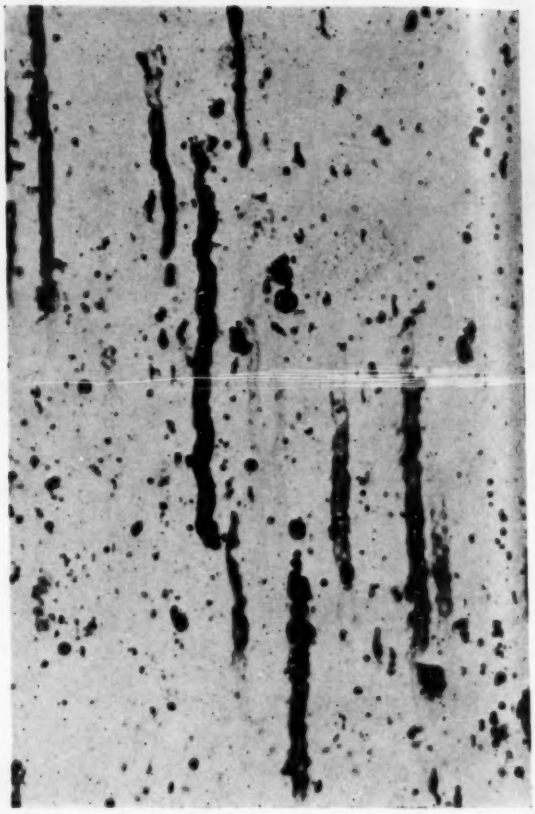


Fig. 11

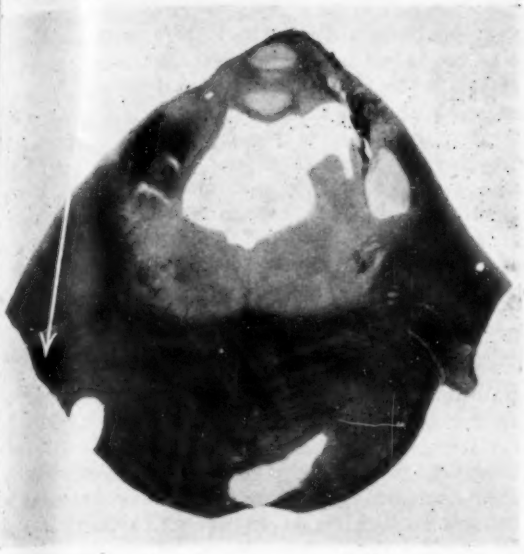
Fig. 9.—True degeneration of fibres (P.O.S. 23 days)

Fig. 10.—True degeneration of fibres (P.O.S. 81 days)

Fig. 11.—Pseudo-Marchi staining of normal fibres.

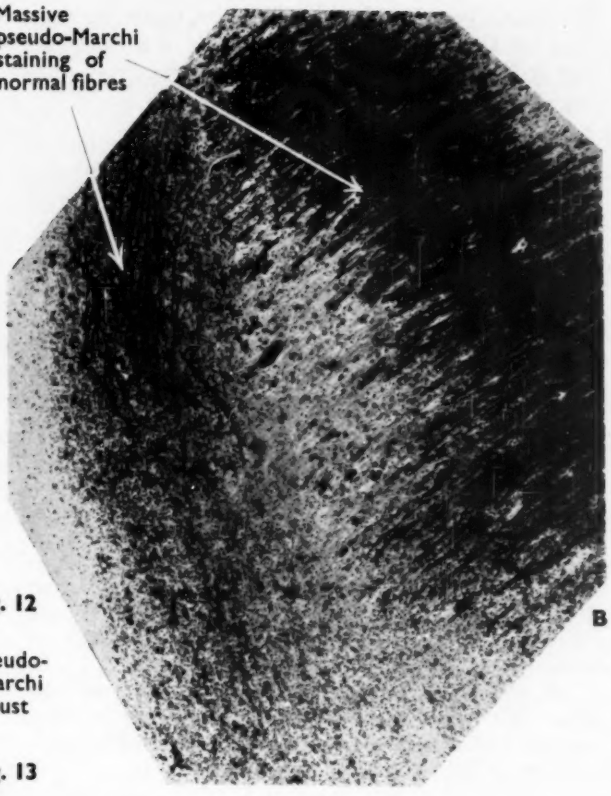
P.O.S. = period of survival

Massive pseudo-Marchi staining



A

Massive pseudo-Marchi staining of normal fibres



B

Fig. 12

Pseudo-Marchi dust

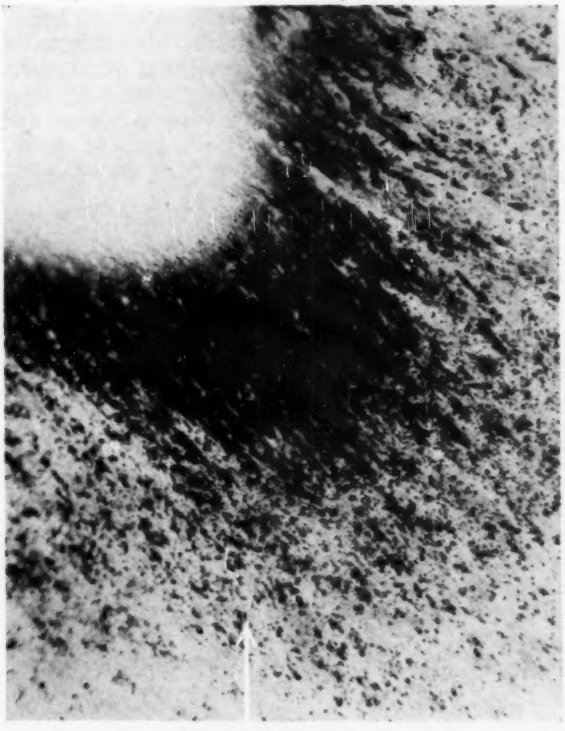
Fig. 13

Massive pseudo-Marchi staining surrounding area of non-penetration

A

Non-penetration of osmic acid fluid

Intense localized staining of fibres



Pseudo-Marchi dust

B

from true degeneration in that the black staining does not spread along tracts or bands of nerve fibres and it is not found in neighbouring sections once the edge of the patch has been reached.

One further feature of Marchi preparations is the occurrence of dark cloudy areas, resulting from irregular depth of staining (Fig. 8). With high magnification, such an area is more deeply stained than the rest of the section, and is brown not black. The appearance in no way resembles degeneration of fibres.

THE PREVENTION OF ARTEFACTS

As was stated above, no method has been discovered by which artefacts can be entirely prevented. There is already a large literature devoted to ways and means of avoiding them. I have found the following papers particularly useful: Duncan (1930, 1931), the latter including a comprehensive review of the literature up to that time; Mettler (1932); Swank and Davenport (1934, 1935); Weisschedel and Jung (1939); Mettler and Hanada (1942). The method of impregnation used on most of the present material is essentially that of Swank-Davenport-Glees (Glees, 1943).

The recommendations given below, unless otherwise stated, are applicable to the Swank-Davenport-Glees method, and also, as far as my experience goes, to other versions of the Marchi technique.

Gentle Handling of the Tissue

At all stages from necropsy onwards extremely careful and minimal handling of the tissue is essential. Even slight tension on nerves must be avoided. In my experience it is immaterial whether the brain and spinal cord are removed in the fixed or the unfixed state: equally good preparations are obtained. It is the gentleness of handling the specimens which is important. At every stage the blocks must be prevented from drying.

Fixation

The length of the period of fixation does not appear to have much influence on the occurrence of artefacts. Contrary to general belief, in tissue stored in formalin for many years artefacts have been consistently absent.

Choice of Size of Blocks

One of the drawbacks of the Marchi method is that the osmic acid solution tends not to penetrate the blocks. In some instances the area which is not impregnated is surrounded by dense artefact formation. Owing to this lack of penetration workers have tended to use small and thin blocks. But when the blocks are too thin there is another difficulty: the tissue is brittle and is inclined to warp. In my experience the blocks must be thin, but they need not be small. Three mm. has proved the best thickness for large blocks, and 5 mm. the best for small blocks.

When selecting blocks of tissue it is important to decide whether it is more desirable to secure an uninterrupted picture of a degenerated fibre and its relations, or to secure a block in which there is definite impregnation at all levels. In some instances it is better to risk non-penetration deep in the block, and to obtain a large section showing all the ramifications of degenerating nerves, than to cut serial sections throughout the block. It should be noted here that non-penetration is not inevitable in large blocks, but the chance of its occurrence is greater. I have obtained good results with blocks measuring 90 × 60 × 3 mm.

Precautions during Impregnation with Osmic Acid

When making up the osmic acid solution, as soon as the capsule of the osmic acid crystals is broken, the crystals must immediately be put into the water and the bottle corked. The reason for this is the rapidity of loss of strength of the acid by vaporizing.

Adequate impregnating solution for the number of blocks is essential, e.g., about 200 ml. to one large block, or 10 small blocks (e.g., transverse blocks from the spinal cord). With large blocks, particular attention has to be paid to ensure that they lie on a flat surface at all stages of preparation. It is essential to avoid superimposition of blocks when in the osmic acid solution. With all blocks better penetration is achieved if they are turned over every two days, so that each side is equally exposed to the solution. This method has been found more satisfactory than suspending the blocks of tissue as some workers have done; this latter method was found to be suitable only when there are a few blocks and when these are small.

As noted by other workers the following precautions have been found to be of value: the tissue, when in the impregnating solution, should be kept in the dark; tight-fitting non-metal tops should be used for the containers of fluid and tissue, in order to avoid any escape of osmic acid vapour, or reaction with the metal.

Treatment after Osmic Acid Solution

As recommended by Swank and Davenport, continuous washing in running water for 24 to 48 hours after impregnation is essential. If celloidin or paraffin preparations are being made, the time taken over each stage of dehydration, clearing, and embedding of the blocks should be the shortest possible.

Advantage of Frozen Preparations

A most important aspect of artefact formation is its absence or infrequence in frozen preparations. The appearance of such sections, compared with adjacent celloidin sections, suggests that dehydration is a frequent factor in the production of pseudo-Marchi artefacts. The following investigation was made to test this. Frozen sections were cut from blocks after treatment with the impregnating fluid, and the block was then dehydrated and embedded in celloidin as usual. The frozen and celloidin sections were then compared. In a number of instances numerous pseudo-Marchi artefacts were found in the celloidin sections, while the frozen sections were

perfectly free from them. For this reason frozen preparations may be recommended for all work utilizing the Marchi method if serial sections of the blocks are not required. When complete series of sections are essential, celloidin preparations are easier to handle.

This brief account of measures found useful in limiting the production of artefacts in Marchi preparations is not a theoretical review of the method, but it is intended to be of some practical value to those inexperienced with the method.

Summary

The Marchi technique remains the best method of demonstrating degenerating nerve fibres within certain limits of time. Recent work has shown that these limits can be extended. The occurrence of artefacts remains the most serious disadvantage of the method.

Illustrations and descriptions of the various forms of artefacts are given, and ways of distinguishing them from true degeneration of nerve fibres are presented.

Some practical precautions in preventing the formation of artefacts are recommended.

I should like to thank Dr. E. A. Carmichael for his encouragement and advice, Mrs. J. A. Mills and Mr. Peter Sharp for all their careful technical work, and Mr. J. A. Mills for his generous help in taking the photographs.

References

Duncan, D. (1930). *J. comp. Neurol.*, **51**, 197.
——(1931). *Arch. Neurol. Psychiat. (Chicago)*, **25**, 327.
Glees, P. (1943). *Brain*, **66**, 229.
Mettler, F. A. (1932). *Stain Tech.*, **7**, 95.
——, and Hanada, R. E. (1942). *Ibid.*, **17**, 111.
Smith, M. C. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 222.
——(1956). *Ibid.* **19**, 67.
——, Strich, S. J., and Sharp, P. (1956). *Ibid.*, **19**, 62.
Swank, R. L., and Davenport, H. A. (1934). *Stain Tech.*, **9**, 11, 129.
——, ——(1935). *Ibid.*, **10**, 45, 87.
Weisschedel, E., and Jung, R. (1939). *Z. Anat. EntwGesch.*, **109** 374.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 84.

STUDIES IN SENSATION : OBSERVATIONS ON THE LOCALIZATION OF THE SENSATIONS OF TOUCH AND PRICK

BY

JOHN MARSHALL

From the Neurological Unit, Northern General Hospital, Edinburgh

The sensory experience commonly referred to as a prick is of great interest, not because of its intrinsic importance, but because of the information about sensory mechanisms which can be obtained from its study. In this paper observations on the ability to localize the sensation of prick are reported and compared with the power of touch localization.

The elicitation of the sensation of prick by means of mechanical stimulation with a needle has the disadvantage that the needle must first make contact with the skin, so that a sensation of touch may confuse observation of the prick. Bishop (1943) devised a means of stimulating the skin by an electric spark; he showed that stimulation at certain points gave rise to a sensation of touch while at other points on the skin a prick was felt. Repetitive stimulation of a "touch spot" gave rise to a sensation of pressure, whereas repeated stimulation of a "prick spot" caused pain. This method of stimulation of discrete spots by an electric spark has been employed in the present study.

Elithorn, Piercy, and Crosskey (1952) studied the ability of patients to localize a touch stimulus applied to the fingers before and after the operation of leucotomy. They showed that before operation localization of touch follows a conceptual pattern of the hand in which all points on the skin are not equipotential. Errors are not made and referred at random but in accordance with this conceptual pattern. The observations which are reported here on the power to localize the sensations of touch and prick will be discussed in the light of the findings of Elithorn and others.

Technique

The observations were made on the dorsal and palmar aspects of the middle phalanges of 22 normal subjects (nurses and medical students). The hand was fixed in a plasticine mould, and eight needles were adjusted so that they made imperceptible contact with the radial or ulnar half of the middle phalanx of each of the four fingers. For testing "prick spots" the dorsum of the fingers was used and for "touch spots" the palmar aspect. This was done because "prick spots" are more dense on the dorsum and "touch spots" on the palmar aspect of the fingers (Bishop, 1943), hence it was considered that a fairer comparison could be made by this means rather than by comparing the same skin area with a different density of "prick" and "touch" spots. The needles were adjusted so that they lay over the appropriate type of spot.

An electric spark, produced by a condenser discharge (Fig. 1), was supplied to each needle as required. The

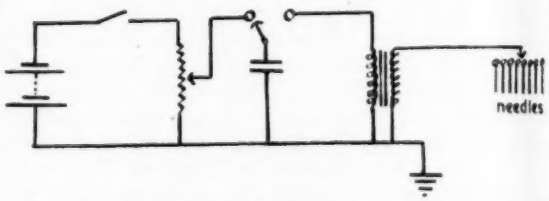


FIG. 1.—Circuit for production of electric spark by means of a condenser discharge through a car induction coil.

hand was screened from the subject, and he was given a diagram of a hand on which to mark his observations. He was instructed to indicate which finger was stimulated, and whether it was the radial or ulnar side. He was not required to indicate the exact site, nor how proximal or distal the stimulus was. Stimuli were applied in a random order, two to the radial and two to the ulnar side of each finger of both hands, making 32 stimuli each for touch and prick. To eliminate the possibility of any learning effects, in half the subjects first the palmar aspect (touch) then the dorsum (prick) of the one hand was tested, followed by the other hand in similar order, while in the other half tests were started on the dorsum of one hand followed by the palmar aspect with the same order in the opposite hand.

Results

Incidence of Errors.—An equal number (704) of stimuli was applied to both touch and prick spots, but as is shown in Table I there were only 143 touch errors but 190 prick errors. Applying a χ^2 test to these figures gave $\chi^2 = 8{\cdot}68$ which is highly significant ($P > 0{\cdot}01$). It immediately appeared,

therefore, that the ability to localize the sensation of prick was inferior to the power of touch localization.

Errors at Different Sites of Stimulation.—When the incidence of errors at the different sites of stimulation was studied (Table I), further differences

TABLE I

NO. OF ERRORS OCCURRING AT EACH STIMULUS SITE IN 22 SUBJECTS

	Sites of Stimulation								
	2R	2U	3R	3U	4R	4U	5R	5U	Total
Touch	6	11	14	35	24	24	14	15	143
Prick	20	16	17	36	28	37	12	24	190

2, 3, 4, 5 indicate index, middle, ring, and little fingers respectively, R=radial side, U=ulnar side in all Tables.

between touch and prick became apparent. In both instances the distribution of the errors could be shown by the χ^2 test to be unlikely to have arisen by chance (touch $\chi^2 = 41{\cdot}68$, $P > 0{\cdot}01$; prick $\chi^2 = 31{\cdot}86$, $P > 0{\cdot}01$), but the distribution between the various sites of stimulation did not follow the same pattern for both types of sensation. In the case of touch, the number of errors rose from both margins of the hand to reach a peak at the ulnar side of the third digit (the middle finger) ; in the case of prick, however, there were marginal peaks on the radial side of the index finger and the ulnar side of the little finger and a central plateau extending over the ulnar side of the middle finger and the radial and ulnar sides of the ring finger. This is unlikely to have arisen by chance as the same pattern was seen on each hand. Hence, though both touch and prick errors appeared not to be distributed by chance but according to a pattern, the pattern was not the same for the two types of sensation.

Sites of Reference of the Errors.—Tables II and III show the sites to which each erroneously

TABLE II

SITE TO WHICH TOUCH ERRORS WERE REFERRED FROM EACH SITE OF STIMULATION IN 22 SUBJECTS

Sites of Stimulation	Sites of Reference of Errors							
	2R	2U	3R	3U	4R	4U	5R	5U
2R	—	6	—	—	—	—	—	—
2U	8	—	1	2	—	—	—	—
3R	1	2	—	8	2	1	—	—
3U	—	1	22	—	5	7	—	—
4R	—	—	4	7	—	13	—	—
4U	—	—	2	2	18	—	2	—
5R	—	—	—	1	—	1	—	12
5U	—	—	—	—	1	—	14	—

localized stimulus was referred for touch and prick respectively. Inspection of these Tables shows that the errors were not referred in a random fashion,

TABLE III

SITE TO WHICH PRICK ERRORS WERE REFERRED FROM EACH SITE OF STIMULATION IN 22 SUBJECTS

Sites of Stimulation	Sites of Reference of Errors							
	2R	2U	3R	3U	4R	4U	5R	5U
2R	—	17	1	1	1	—	—	—
2U	10	—	—	6	—	—	—	—
3R	—	1	—	10	5	1	—	—
3U	—	—	21	—	8	7	—	—
4R	—	—	—	7	—	21	—	—
4U	—	—	1	5	29	—	1	1
5R	—	—	—	—	—	6	—	6
5U	—	—	—	—	1	1	22	—

but were distributed according to a pattern. In every instance for both touch and prick, the majority of errors were referred to the wrong side of the stimulated finger. In the case of touch, in all but two instances (2U, 3U), more errors were referred to either of the two immediately adjacent sites than to more remote sites, while for prick this was so in all but one instance (2U). In this regard the findings differ from those of Elithorn and others (1952) who found that in the majority of instances more errors were referred to the corresponding side of the adjacent finger, that is to a position two removed from the site of stimulation, than to the wrong side of the stimulated finger.

Hence the pattern of distribution of errors was seen to be, first, to the wrong side of the stimulated finger, secondly, to the adjacent side of the next finger and, thirdly, to the corresponding side of the adjacent finger and rarely to more remote sites.

Type of Error.—Two types of error in reference to the site of stimulation may be considered, namely, those arising following stimulation of the ulnar side of a finger and those following radial stimulation. Table IV shows a predominance of

TABLE IV

NO. OF FINGER AND SIDE ERRORS IN RELATION TO SITE OF STIMULATION IN 22 SUBJECTS

	Finger	Side	Total
Prick			
Ulnar	31	93	124
Radial	23	70	93
Total	54	163	217
Touch			
Ulnar	23	73	96
Radial	19	51	70
Total	42	124	166

errors following ulnar stimulation over those following stimulation of the radial side of a finger for both touch and prick. Errors may also be considered in accordance with their site of reference.

Thus, errors may be referred either to the wrong finger or to the wrong side of a finger. The double error of wrong finger and wrong side is considered as two separate errors. Table IV shows that side errors are much more common than finger errors for both touch and prick and, moreover, that both types of error occur more frequently following stimulation of the ulnar side of a finger than the radial. The sites of reference of the two types of error do not appear to follow the same pattern (Table V).

TABLE V
SITES OF REFERENCE OF FINGER AND SIDE ERRORS IN 22 SUBJECTS

	Sites of Reference of Errors							
	2R	2U	3R	3U	4R	4U	5R	5U
Touch								
Finger	1	3	7	12	8	9	2	—
Side	8	8	25	16	24	15	16	12
Prick								
Finger	—	1	2	19	15	15	1	1
Side	10	18	22	18	38	28	23	6

Finger errors are referred almost exclusively to the digits 3 and 4, whereas side errors, though showing a preference for digits 3 and 4, are frequent in digits 2 and 5 also. This feature applies to both touch and prick errors.

Direction of Errors.—The direction of reference of finger errors has been considered in relation to digits 3 and 4, in each of which there is a freedom to refer the error in either a radial or an ulnar direction. Table VI shows that for both touch and prick in the case of digit 3 there is a marked tendency to refer stimuli in an ulnar direction. In the case of digit 4, the opposite tendency prevails. The majority of stimuli are referred towards the radial side of the hand. Thus it appears that when there is freedom of choice, errors tend to be referred towards the middle two fingers, and this tendency is seen to obtain for both prick and touch errors.

TABLE VI
DIRECTION OF REFERENCE OF FINGER ERRORS FOLLOWING STIMULATION OF DIGITS 3 AND 4 IN 22 SUBJECTS

	Referred Ulnarly	Referred Radially
Digit 3		
Touch	15	4
Prick	21	1
Digit 4		
Touch	2	15
Prick	2	13

Discussion

These studies on the ability to localize the sensations of prick and touch may first be compared with those of Elithorn and others (1952) on touch localization. It should be remembered that the experimental methods were similar but not identical in the two series. Elithorn and others used a blunt point to test touch but in this study an electric spark was employed. Elithorn's subjects plotted their results on the hand of an observer, and not on a chart. The number of subjects was the same in both series, but Elithorn was able to examine each many times over a period, and hence has more raw data to analyse. His subjects were, however, admittedly not normal from the psychiatric viewpoint though "most were free from neurological lesions".

The general pattern of the distribution of touch errors in relation to the site of stimulation was the same in both series with a maximum incidence on the ulnar half of the middle finger. The greater liability to error when the ulnar side of the finger was stimulated and the predominance of side errors over finger errors were also features of both series. It was with regard to the sites to which errors were referred that a difference appeared. Elithorn and others found that an error was most commonly referred to the corresponding side of the next finger, rather than to the opposite side of the same or adjacent fingers. In the present series, however, there was a clear tendency to refer errors first to the opposite side of the same finger, secondly to the adjacent side of the next finger, and only thirdly to the corresponding side of the adjacent finger. In both series, however, the results were clearly distributed according to a conceptual pattern and not by chance, but the type of pattern revealed differed in the two series.

When the results for touch and prick are compared in the present series interesting differences become apparent. The superiority of tactile localization over the localization of the sensation of prick is clearly demonstrated. The idea that the sensation of prick is simply touch plus a localized pain is therefore not supported, for, were this so, one would expect the power of localization to be equally good. A further difference is in the abrupt rise in the incidence of errors at the marginal sites of the hand, that is, the ulnar side of the fifth digit and the radial side of the second digit. This was found for both hands separately, hence is unlikely to have been an artefact, and is in contrast to the finding in the tests on touch localization. This suggests that prick is dealt with separately from touch not only with regard to the immediate appreciation of its distinctive quality, but also with regard to the recognition of its site of origin.

That the mechanisms which enable us to recognize a sensation are separate from those subserving its

localization is clearly demonstrated by the abolition of the power of localization without impairment of appreciation of touch in lesions of the parietal cortex. It might be thought, however, that though the mechanisms for the appreciation of the various modalities of sensation are different, all localization is carried out by a single mechanism fed by information from the primary sensory areas. The degree of accuracy of localization achieved for each modality would depend on the amount of sensory information supplied to the localizing mechanism.

The differences in the incidence of errors of localization of the sensations of touch and prick as shown in this study, however, were not only of degree but also of kind. Prick was not only less accurately localized, but the incidence of errors followed a different conceptual pattern showing peaks at the margins of the hand as well as the centre. A point in the skin did not therefore have the same " value " for the localization of both touch and the sensation of prick. It would seem, therefore, that the mechanism underlying the power of localization is not simple but complex, and that separate mechanisms subserve the localization of touch and the localization of the sensation of prick. Differences in the powers of localization of various sensory modalities might well, therefore, be sought in discrete lesions of the parietal lobe.

Summary

Localization of the sensation of touch is superior to that of prick.

Both the incidence of errors at each site of stimulation and the way in which errors are referred appear to follow a conceptual pattern, but the pattern is not identical for touch and prick sensation. This suggests that the localization mechanism for the sensation of prick is distinct from that for touch.

I wish to thank Dr. P. E. Brown for statistical advice.

References

Bishop, G. H. (1943). *J. Neurophysiol.*, 6, 361.

Elithorn, A., Piercy, M. F., and Crosskey, M. A. (1952). *Journal of Neurology, Neurosurgery and Psychiatry*, 15, 272.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 88.

REFERENCE OF SENSATION AT THE SPINAL LEVEL

BY

P. W. NATHAN

From the Neurological Research Unit of the Medical Research Council, National Hospital, Queen Square, London

After the spino-thalamic tract has been cut in man, loss of sensation of pain and temperature caudal to the lesion is to be expected. In a small proportion of patients, although analgesia—in the usual sense of the term—is present, painful or thermal stimuli applied to parts of the body caudal to the lesion arouse a sensation, which is felt, not at the place actually stimulated, but in a normally innervated part of the body. Thus, a pin applied to the analgesic left leg, for instance, may cause a sensation referred to the normally innervated right leg.

This form of reference of sensation following the cutting of the spino-thalamic tract on one side of the cord was described by Ray and Wolff in 1945. A somewhat similar phenomenon had previously been described by Obersteiner in 1881, and named " allochiria ". In Obersteiner's cases, the phenomenon consisted of a difficulty in localizing the site stimulated rather than a definite reference. Obersteiner's reference of sensation consists of " the fact that though the sensibility is retained more or less completely, yet the patient is not clear, or is frequently, if not constantly, in error, as to which side of the body has been touched ". A condition more like that described by Ray and Wolff had been studied in monkeys by Mott in 1892. He found that after a hemisection of the cord stimuli applied to one side were apparently felt as though they had been applied to the other.

In spite of these early observations this phenomenon has awakened little interest. Ray and Wolff, for instance, seem not to have known that a similar phenomenon had already been observed.

In my experience the reference of sensation described by Ray and Wolff is a part of a more general phenomenon. In patients with division of one spino-thalamic tract there may be reference not only to an analogous place on the opposite side of the body, but cranially, caudally, and in more complicated ways. Further, the reference may occur following division of both spino-thalamic tracts. It may also occur without the division of any tracts.

The purpose of this paper is to describe the features of such reference of sensation and to record it in conditions other than in those previously reported. Certain related phenomena will also be described. An investigation of the various forms of the reference of sensation will be reported ; and the possible underlying mechanism and the anatomical implications will be considered.

Observations

This reference of sensation has been observed in one patient having an amputation of an upper limb, in one patient with a thrombosis of the anterior spinal artery, and in 13 patients following antero-lateral cordotomy. The observations on the amputation case, the case of anterior spinal artery thrombosis, and six cases of cordotomy will be given in some detail ; the findings in the other seven patients will not be given, as they are similar to those of the other cases.

There are certain broad patterns of the mode of reference of the sensation. Any one form or any combination of the forms of reference may occur in any one patient. There may be a reference from the analgesic side to the analogous place on the opposite side of the body, there may be reference cranially or caudally to normally innervated parts of the body, there may be a spread of sensation felt as coming from the place stimulated ; there may also be a reference to one constant region of the body of all stimuli applied to the analgesic parts.

Case 39*.—An antero-lateral cordotomy was performed on the left side of the cord at the second cervical segment. This produced analgesia throughout the right side of the body below the second and third dermatomes.

Forty hours after the operation it was observed that the sensation from a pin of 140 g. weight was referred from one side of the body to the other. This was suspected by the examiner, for when the pin was applied to the analgesic right side, the patient immediately put up his hand and covered an analogous place on the left side of the chest. When he was asked why he did this, he

* The numbers of the cases are the same as those used throughout the series of papers by Nathan and Smith.

replied that he did not know. On every occasion that he was pricked on the right side of the chest, he always put his hand up to rub the left side. Eventually he said that he could hardly believe his senses, but it seemed to him that he felt the pinprick applied to the right side of the chest as though it were on the left.

The following forms of stimulation caused this reference of sensation: pinprick of 140 g. weight; pinching the skin; pressure with an algometer of 20 lb. weight; a test-tube of water at 60° C. (but not at 50° C.); spraying the skin with ethyl chloride; squeezing muscles. The nature of the sensations induced by these various stimuli was not the same regardless of the nature of the stimulus and was not what would have been expected from the nature of the stimulus. Pinprick applied to the right side of the chest was felt on the left as the sensation of an electric shock on some occasions, on others as a pinprick; pressure with the algometer on the right felt like an electric shock on the left, only more painful; on other occasions it felt like painful pressure; water at 60° C. applied to the right side of the chest felt on the left either like pressure or "a soreness"; ethyl chloride applied to the right felt on the left like tickle or like cold; pinching the skin on the right felt like a pinprick on the left; and pinching the whole thickness of the axillary fold felt on the left painful, "in the same way as tapping a bruise is painful". The most striking feature of all sensations referred to the left was that they were felt to come from within. Stimuli applied to the right side of the chest were felt on the right as coming from without, in the normal way; but the stimuli applied to the right side of the chest were felt on the left as though the stimulus had been applied inside on the left; it came from within outwards. The patient could be made to have the sensation of pinprick on the left side by the pin being applied either on the left or the right; however he could always tell which side had in fact been stimulated, as when the left side was actually pricked he felt the pinprick coming from without, whereas when the right side was pricked, he felt the sensation on the left coming from within. When he was pricked with a 5-g. pin on the left, he felt this in a normal manner; when he was pricked with a 50-g. pin on the right, he felt this as touch on the right and as a pinprick coming from within on the left. These two stimuli were then applied simultaneously in analogous positions. The patient then felt on the left a pinprick coming from outside, and noticed nothing on the right. Thus the 5-g. pin on the left preponderated over the 50-g. pin referred from the right. It was possible to deceive the patient by the use of bilateral simultaneous stimulation. For example, a touch stimulus applied to the left and a prick stimulus to the right gave sensations of pinprick on the left and of touch on the right. With suitably weighted pinpricks, bilateral simultaneous stimulation could be applied so that only touch was felt on the right and two pricks were felt on the left, the one coming from outside and the other from inside.

Fig. 1 shows the region of the body from which stimulation was referred to an analogous place on the opposite side. The upper limit was the second intercostal space. The nearer the stimulus was applied to this upper limit, the more easily it was referred; thus only a slight stimulus would evoke the referred sensation, and the referred sensation was felt more clearly and more quickly. Stimuli, however, were not invariably referred to the opposite side of the body; on one or two occasions hard pressure applied by the algometer on the right side gave a sensation on the same side, referred cranially to the normally innervated segment of the neck.

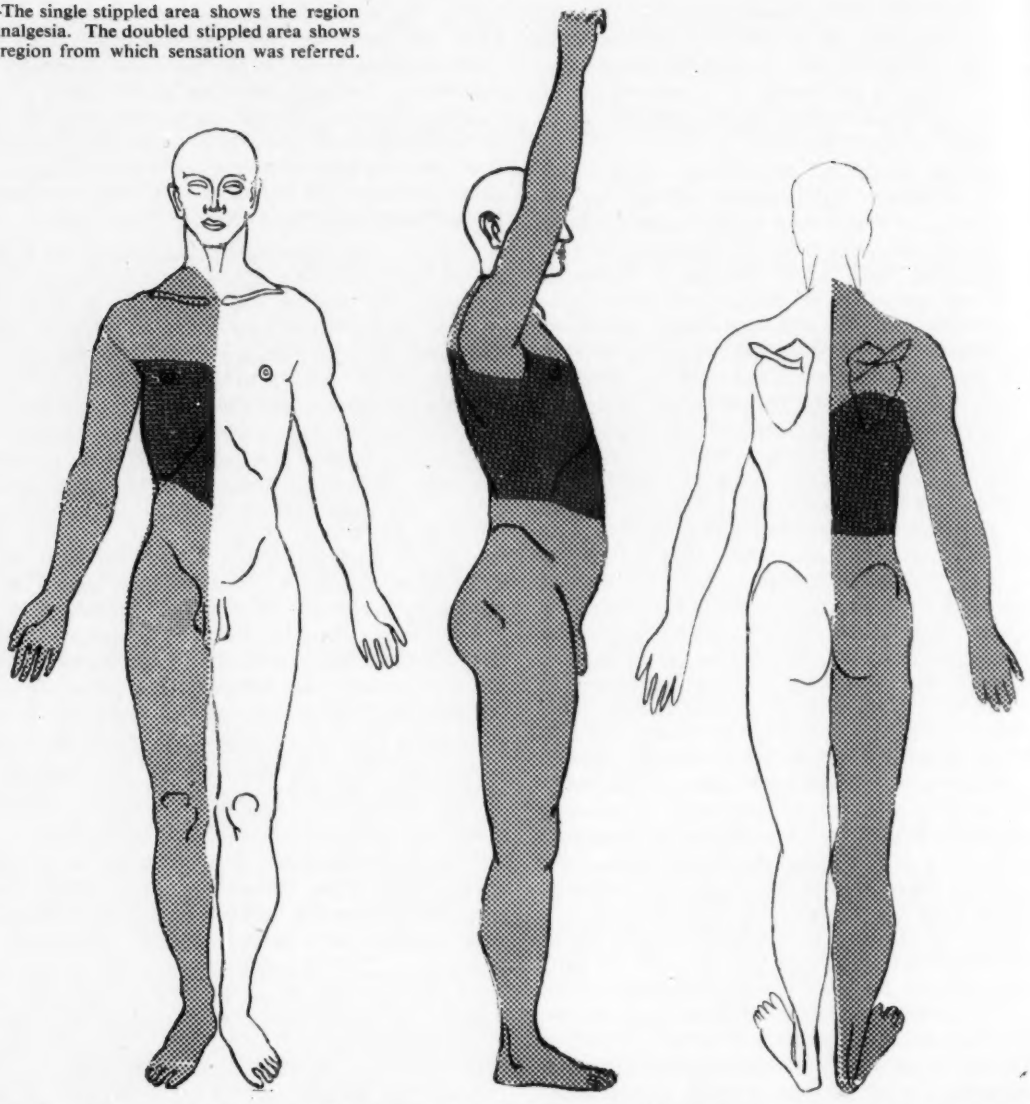
Case 11.—An antero-lateral cordotomy was performed on the right side of the cord at the sixth thoracic segment and a similar one on the left at the seventh thoracic segment. For about three months following the operation there was analgesia to heavy pinprick throughout the left side of the body up to the lower border of the ninth thoracic dermatome and throughout the right side of the body up to the lower border of the second lumbar dermatome. After that time, the sensibility recovered on the right, so that there was no total loss of pain sensibility; the upper border of diminution of sensibility remained as before; when deep pressure was used as the painful stimulus, it was found that there was only hypoalgesia throughout the right lower limb. There was no change in the loss of sensibility on the left.

A fortnight after the cordotomy, pressure applied by the algometer was felt in the following way. When it was applied to the left buttock or the left tendo Achillis, the painful sensation was referred to an area in the left chest wall, about 6 in. caudal to the axilla; this was within the region of the girdle distribution of pain and tenderness which followed the operation. When it was applied anywhere on the right lower limb, it was referred to the region of the right patella; even when applied to the right popliteal fossa, it was still felt in the region of the patella, in front of the limb. Thus, on the right, the pain of the stimulus was felt in the knee, whether the stimulus was applied cranial (lumbar 1 and 2) or caudal (sacral, 1, 2, 3, or 4) to the segmental nerve supply of the knee. The patient said that these stimuli which were referred to the knee were referred to the identical place at which she had had pain years before. At that time she had been involved in an accident and had a painful comminuted fracture of the right patella. After the patella had been excised, the pain had gone, and she had forgotten about the whole incident. The reference of the painful pressure with the algometer, however, had produced the same pain in the same place, and had forcibly reminded her of the previous damage to her knee.

Placing her lower limbs in water at 60° C. also caused reference of sensation. It caused a sensation as though the limbs had been put in electrically charged water. On the right this electric shock feeling shot to the knee; on the left it shot up to the girdle region of tenderness. There was no sensation of burning or warmth. This reference of the sensation is shown in Fig. 2.

Case 32.—An antero-lateral cordotomy was performed on the right side of the cord at the seventh thoracic segment. It produced analgesia throughout the left side of the body up to the lower border of the seventh thoracic dermatome.

FIG. 1.—The single stippled area shows the region of analgesia. The doubled stippled area shows the region from which sensation was referred.

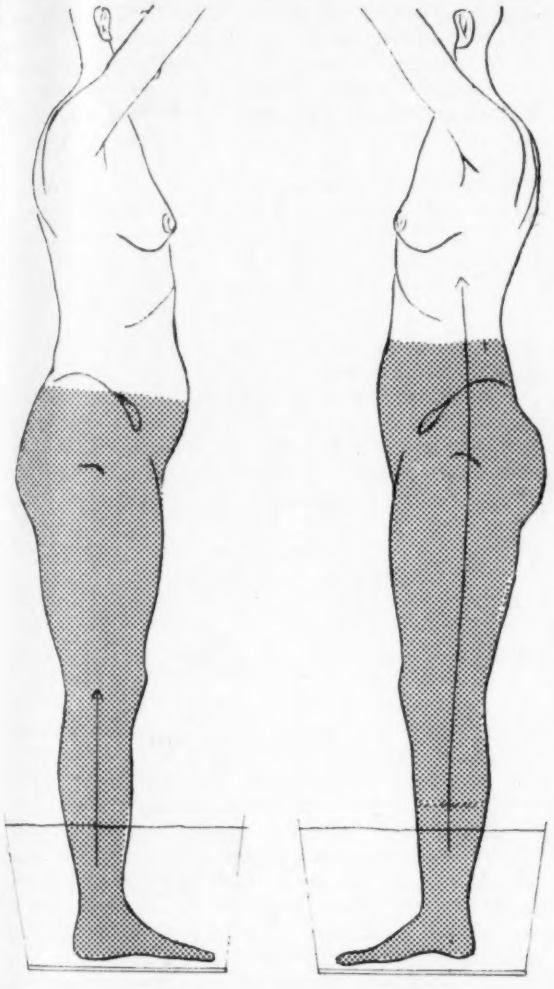


Twenty-four hours after the operation it was found that the sensation from a pin of 140 g. weight was referred from the left groin towards the back or cranially ; locally this stimulus was felt as touch. Twenty-four hours later pressure with the algometer was referred from the back of the left thigh to the back of the right thigh, and from the left iliac crest cranially on the left to an area immediately cranial to the limit of the analgesia area. At the places where these stimuli were actually felt they felt like pinpricks ; at the places where they were applied they were felt as painless pressure. On the next day it was observed that pins of 90 and 140 g. weight applied just caudal to the inguinal ligament were felt as pinpricks just caudal to the left scapula.

By the tenth day after the operation the region of analgesia had diminished so that pinpricks of 140 g. weight were felt above the tenth thoracic segment. If such a prick were applied at the place where this region of analgesia merged into the region of hypoalgesia above, then it was felt as a prick both at the place at which it was applied and in the region of the left scapula. Caudal to this region pricks were felt locally as touch, while the pain was referred cranially to the left thoracic cage in the axillary line.

A fortnight after the operation rapidly repeated hard pinpricks to the lower quadrant of the left side of the abdomen or to the anterior surface of the left thigh were felt in the same place in the left side of the chest immediately cranial to the upper boundary of the region of hypoalgesia. It became apparent that there was a region on the left side from which all painful stimuli were most easily referred : this region overlapped the twelfth thoracic dermatome by an inch or so cranially and caudally ; it stopped at the midline. Stimuli applied here caused " a strange feeling "—the patient could not say more than this. At the region to which the painful

FIG. 2.—The stippled area shows the region of analgesia. The feet are shown in buckets of water at 60° C.



stimuli were referred, they felt like a pinprick, yet more diffuse and deep inside ; when the stimulus was repeated rapidly, it felt like a single continuous painful pricking. The reference of the sensation was not in the same plane cranio-caudally ; on most occasions stimuli applied anteriorly were felt cranially in a more posterior plane.

Ten weeks after the first cordotomy, another one was performed on the other side of the cord at the second thoracic segment. Following this operation there was on the right side of the body very marked analgesia up to the lower border of the second thoracic dermatome ; on the left side there was marked analgesia up to the lower border of the eleventh thoracic dermatome, and complete analgesia up to the lower border of the twelfth thoracic dermatome.

The manner in which repeated heavy pinpricks were referred is illustrated in Fig. 3. Stimuli applied to the territories supplied by the lower lumbar or the sacral nerves were not referred. The region to which the stimulation was referred was usually a constant area ; it was a band running cranio-caudally immediately posterior to the anterior axillary line. Eventually there developed at this region a spontaneous tingling, present all the time ; and this region became tender to pressure.

One month after the second operation, 400 ml. of fluid was run by drip into the patient's bladder. As the amount and the pressure increased, she got the pain in the usual place over the left ribs ; when the bladder was emptied, this pain was relieved.

About six weeks after the second operation all stimuli giving rise to impulses normally conducted by the spino-thalamic tract produced a sensation in this same area in the left side of the thoracic cage. The reference was most easily obtained ipsilaterally, a stronger stimulus being needed on the right to cause it. Usually the stimulation was felt as running up to this region in the left side of the chest ; for example, if pressure was made with the algometer, it was not felt as long as the pressure was very light ; as the pressure was increased, the sensation was felt travelling up to the region to which sensations were referred ; further pressure produced more intense pain in this region ; it did not travel further cranially. The reference was most easily obtained by using a cold stimulus, such as ethyl chloride spray ; it was also obtained by pinprick, algometer, the application of hot water, or by distending the bladder; it was not obtained by injecting 5% saline.

Two weeks later cystometrography was repeated. After 300 ml. of fluid had been run into the bladder, 0·25 mg. of carbaminoylcholine was injected intramuscularly. As the pressure slowly rose, she got the pain in the usual place in the left side of the chest. The pain started as the pressure reached 25 cm. of water ; at a pressure of 31 cm. it was severe. These pressures were associated with only 250 to 300 ml. of fluid in the bladder. The sensation felt in the left side was " a painful twisting feeling ". It did not go off immediately the bladder was emptied. Thus a quite usual amount of fluid in the bladder held at a physiological pressure caused pain referred to the constant region. Stretching the anal ring only slightly more than might normally occur brought on a pricking pain in the same place on the left side.

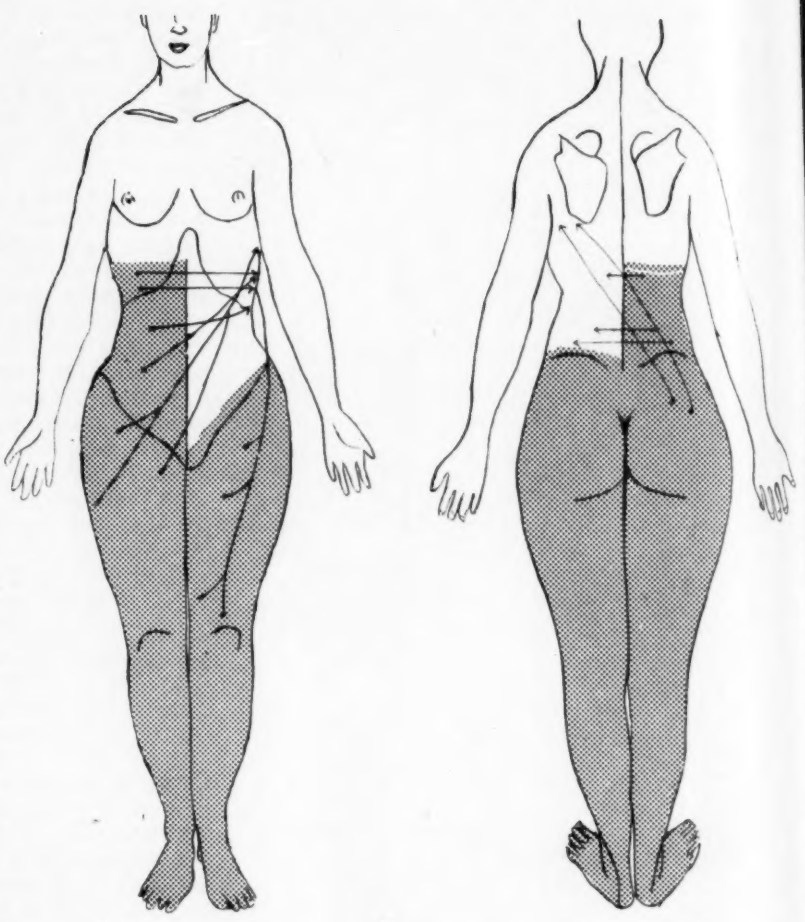
An experiment was carried out consisting of anaesthetizing that region to which sensations were referred. Following the injection of 8 ml. of 1% procaine, there was no longer any local tenderness. As long as this region remained anaesthetic, there was no reference of sensation. This experiment was controlled in two ways : on another occasion 8 ml. of 1% procaine was injected into the buttock ; reference of sensation occurred as usual, showing that this amount of procaine had no general effect in stopping the reference of sensation ; on another occasion, the tender area was injected with normal saline, the patient being told that it was the same experiment as before ; however, on this occasion, there was the usual reference of sensation.

The area in the left side of the chest to which the sensation tended to be referred was in itself not apparently abnormal, apart from being somewhat tender to pressure. No abnormalities were revealed by radiography, and at necropsy nothing abnormal was found.

Case 38.—An antero-lateral cordotomy was performed on the right side of the cord at the third thoracic segment. It produced some impairment of pain sensibility up to the lower border of the third thoracic dermatome, much impairment of pain sensibility up to the fifth thoracic dermatome, and total analgesia to all forms of painful stimuli up to the lower border of the eleventh thoracic dermatome on the left.

About a fortnight after the operation the patient gradually became aware of an uncomfortable sensation over the posterior part of the right ilium. This developed so that it eventually became the identical pain that she had had on the left before the operation, felt in the same region but on the opposite side of the body. It was not due to any sudden spread of the cancer involving the nerves or the bones on the right. Five weeks after the operation it was found that pressure with the algometer on the anterior, lateral, and posterior aspects of the left thigh, and in the left popliteal fossa caused a reference of sensation to an area on the posterior aspect of the right ilium : this region was that where she had previously complained of the spontaneous pain developing after the operation. Over the next few days this spontaneous pain became more severe, and its area became more extensive, so that it involved also the right thigh. At this stage, all large active or passive movements of the left lower limb caused pain referred to the painful area on the right ; the movements most likely to cause this referred pain were flexion of the lower spine, and flexion, extension, and adduction of the left lower limb. It is to be noted that although such movements may well have stretched the right sacro-iliac joint or the attachments of the ilium to the sacrum, any movements of the right lower limb designed to cause pain in the ilium failed to do so ; thus we had the paradoxical position of being able to cause pain in the right iliac region by large movements of the left lower limb, whereas we could not cause pain in the right iliac region by similar movements of the right lower limb.

FIG. 3.—The stippled area shows the region of analgesia.



The experiment was performed of anaesthetizing with 1% procaine the area to which pain was referred. However, it was unsuccessful, in that the whole region, which by this time took in the whole of the inguinal region and the right ilium, was not rendered anaesthetic. Following the injection, the reference of the stimuli occurred largely to those regions that had not been properly anaesthetized. Pain from large movements of the spine at the left lower limb was still referred to the deeper parts of this region that remained unanaesthetized.

Once this reference of sensation had become established, it gradually became easier to elicit it. At first it needed at least 40 lb. pressure with the algometer to cause it ; eventually it appeared with only 20 lb. At first stimuli were referred only when they were applied to the totally analgesic region ; eventually stimuli were referred when they were applied to hypoalgesic regions, such as the left side of the abdomen. Such stimuli were thus referred across the midline and caudally. No stimuli applied to the right normally innervated side of the body were referred.

Twelve weeks after the first operation a further antero-lateral cordotomy was performed on the left side of the cord at the sixth thoracic segment. It produced some impairment of the sensibility of pain up to the lower border of the fifth thoracic dermatome, and complete analgesia below the lower border of the first

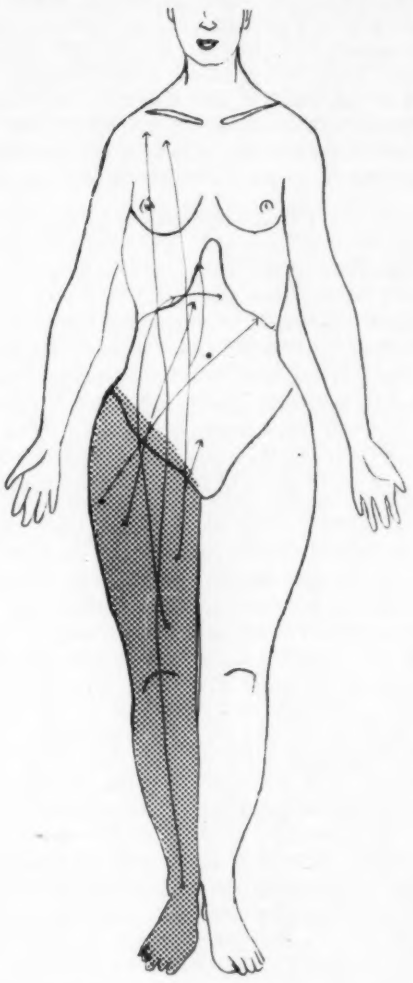
lumbar dermatome. Painful pressure in the most cranial part of the totally analgesic area on the right was now referred upwards to the partially analgesic area on the right, just above the inguinum and around the iliac crest. This second operation removed all her spontaneous pain, and it was no longer possible to get reference of pain to the right from stimulating any part of the body on the left.

Case 54.—An antero-lateral cordotomy was performed on the right side of the cord at the first cervical segment. It produced complete analgesia throughout the left side of the body up to the lower border of the fourth cervical dermatome, and hypoalgesia up to the lower border of the fifth cranial nerve territory.

Within three days of the operation it was found that painful pressure applied to the analgesic area was felt as though it came from an identical spot on the opposite side of the body. The following forms of stimulation caused a reference of sensation to the normally innervated side : painful pressure ; pinprick ; slight pinching, just enough to cause pain in normal areas ; smacking, also just enough to cause pain ; stretching the skin by fixing it firmly and then dragging a finger firmly along the stretched skin. Spraying with ethyl chloride in this case did not cause reference of sensation. The region from which stimulation was referred extended from the second rib above to the knee below. On the right side of the body, at the places where the sensations were felt, the nature of the stimulus felt always the same, regardless of the actual kind of stimulation ; the patient stated that had he got only the right side of the body from which to judge the nature of the stimulus, he could not tell what was the nature of the stimulus. On the right stimulation felt like " a tearing kind of pricking " and it felt as though it came from within outwards. The reference of the sensation was roughly to the same place on the right side of the body, but it was not always exactly the analogous place. Stimuli applied to some areas on the left were referred to quite a different place ; for instance, squeezing the left abdominal wall gave a pain in the region of the bladder on two occasions ; on other occasions it was referred to the analogous place to where it was applied on the right abdominal wall. Squeezing the left thigh on one occasion gave a sensation in the right thigh, but on another occasion it gave the feeling that he needed to micturate.

An experiment was performed of inducing a tender and painful area on the right side, for it was desirable to know if a painful area could mop up—so to speak—stimuli from the other side. A quarter of a ml. of 6% saline was injected into the right pectoralis major ; this caused local pain. The various kinds of stimulation which previously caused reference were then applied to the left side of the chest. It was found that they were not referred to the tender and painful area on the right, unless they were applied in the same dermatome on the left. This experiment was repeated, the saline being injected on this occasion into the right rectus abdominis. Stimuli were not referred to this region of induced tenderness. Thus it was concluded that an area artificially and temporally made tender did not serve as a region to which painful sensation was referred.

FIG. 4.—The stippled area shows the region of analgesia.



Case 41.—An antero-lateral cordotomy was performed on the left side of the cord at the sixth thoracic segment. It produced total analgesia throughout the right side of the body up to the lower border of the twelfth thoracic dermatome, and hypoalgesia up to the lower border of the tenth thoracic dermatome.

Before this operation the pain had been throughout the right lower limb and of a deep aching and burning kind ; after this operation, this identical pain was felt in the left lower limb. The patient observed this shift of the pain from one limb to the other as soon as she came round from the anaesthetic.

No reference of sensation was found when heavy pinpricking was used ; but painful pressure with the algometer caused reference of pain. The stimulus was felt to spread in a diffuse unlocalized manner, illustrated in Fig. 4., as an unpleasant form of tingling. Many of the stimuli were felt in the right hypochondrium, and

travelling from here to the epigastrium and the left hypochondrium ; this was the region where she had the common girdle pain that occurs after the operation. Hyperextension and rotation of the right foot caused reference of the pain ; it caused a tight feeling where the girdle pain was situated, and it also caused pain in the region of the trochanter of the left femur, that is, in a region identical with that in which she had previously had the pain on the right for which she had the operation.

Case 9.—A thoraco-lumbar sympathectomy was performed in this patient in two stages. During the second operation, performed one month after the first, the patient became very shocked. When she recovered from the anaesthetic, it was apparent that she had a thrombosis of the anterior spinal artery. This diagnosis was eventually confirmed histologically 10 months later.

There was analgesia below the lower border of the twelfth thoracic dermatome bilaterally. All pricks of 140 g. weight or deep pressure applied with the algometer were referred cranially to the normally innervated parts of the body. In this patient no stimuli were referred across the midline. For instance, pressure applied to the anterior surface of the lower part of the right leg was felt in the inner part of the right inguinal region ; and pressure at the same spot on the left was referred to a place just to the left of the umbilicus. Pressure applied to the right calf was felt in the right breast, and pressure to the back of the right thigh was felt just below the right breast. Pressure on the back of the left thigh was felt just below and to the left of the umbilicus. Pressure just below the middle of the right iliac crest was felt just above the iliac crest, on the right, posteriorly. The principle of the reference was that the more severe the stimulus, the further cranially it was referred ; and when the stimulus was applied gradually and slowly, it was felt as travelling up the body gradually and slowly. Although the stimulus was not referred across the midline, it was not felt necessarily in the same vertical plane. At the place at which the sensation was felt it had the character of a deep pinprick, regardless of the nature of the actual stimulus.

Case 62.—This man, in May, 1953, had an amputation of the left upper limb. Within nine months of the operation he developed intense pain and involuntary movements in the stump. This pain consisted of a burning ache deep inside the stump ; in addition, there was on certain occasions, the sensation as though boiling water were dripping on to him ; when this pain continued for long, he would get nauseated and vomit.

I first saw the patient in March, 1955. He was more or less free from pain when he was sitting naked, there being nothing touching his stump or the upper part of his body on the left ; but the slightest touch or even a puff of air on the front of the chest on the left gave him severe pain. He had himself found that touches anywhere on the left above the level of the umbilicus were immediately felt above the left nipple ; simultaneously he would get a shooting forward of the stump, and the pain of the boiling water being dripped on to it.

I found on examination that many stimuli were referred to an area above the left breast, mainly in that region of skin forming the border between the fifth cervical and the third thoracic dermatomes. The referred sensation was felt as something burning hot and moving inside ; a single stimulus would be felt at the place of reference for 20 to 30 minutes ; if successive stimuli were applied, he could not feel them individually at the place to which they were referred, having then a sensation of continuous burning movement. The stimuli referred were not necessarily of a noxious character. For instance, touches applied to the right breast with a nylon No. 1 hair were clearly felt on the left as little burns. Touches on the stump with a nylon No. 3 hair were felt on the stump as little pinpricks, and in the left side of the chest as little burns. All stimuli that were referred gave the sensation of a little explosion of burning, coming from within outwards. The places from which stimuli were referred were the left side of the face, both sides of the neck, the stump on the left, the right side of the chest, and both sides of the abdomen. There was a gradation of ease of reference ; on the face, the stimuli had to be more severe on the forehead than on the cheek or mandible in order to be referred ; on the abdomen, they were more easily referred from the left side than the right ; of all places, they were most easily referred from the posterior part of the stump. There was no reference of sensation from the lower limbs. Stimuli that are normally painful were not those most easily referred : spraying the skin with ethyl chloride (a stimulus purely of cold) most easily caused reference, and at the place to which it was referred, it caused more pain than any other form of stimulation.

In addition to this reference of sensation, there was over the front of the left chest, at the place to which sensations were referred, a great lowering of threshold for all forms of stimulation, and also a perversion of sensation so that even the lightest touches evoked pain. For example, on the right chest, touches with nylon hair No. 1 (weight, 0·004 g.) were felt 16 of 20 applications, the patient being often uncertain whether he felt them or not ; on the left side of the chest, he felt 20 out of 20 applications, and he felt them easily ; but on the left they were felt as little burns, and not as touches. Moving the axillary hairs on the left caused local burning pain, and touching the stump with a nylon No. 3 hair gave a local sensation of pinprick (as well as the reference mentioned above). Such stimuli as these cannot have stimulated " pain nerve endings " ; one must conclude that stimulation of " touch endings " may cause this burning pain.

The experiment was performed of inducing a small local region of temporary severe pain. One-third ml. of 6% saline was injected into the ligaments of the spine below the seventh cervical vertebra. It caused no local pain, but increased the pain in the stump and in the region in the front of the left side of the chest to which sensations were referred ; it did not change the reference when stimulation was applied to other regions ; ethyl chloride, for instance, sprayed on the right side of the chest, the neck, or the left side of the abdomen, was still felt in the left side of the chest.

The sympathetic chain was injected on the left. It caused a Horner's syndrome and vasodilatation on the left side of the head and neck. This injection with procaine reduced the spontaneous burning to slight, and took away the spontaneous jactitation of the stump. It did not stop the reference of sensation, although it removed its sensitivity and the ease with which it could be obtained. This injection was controlled on another occasion by injecting saline instead of procaine ; this had no effect whatsoever.

On a further occasion the left supraclavicular nerves were injected with procaine. This reduced the severity of the pain in the left side of the chest, but the stump remained as sensitive as before. There was no reference of sensation to the anaesthetic area ; but there was still reference to the area caudal to the anaesthetized region ; also, the region deep to the anaesthetized skin remained tender. The blocking of the sympathetic chain was far more effective than the blocking of the supraclavicular nerves in alleviating the pain and in reducing the reference of sensation.

Summary of Observations

The material presented here consists mainly of cases of division of the spino-thalamic tract. There was also one case in which there was no gross anatomical lesion of the tracts of the central nervous system, but an amputation of a forelimb ; this may be seen as an example of a complete peripheral nerve lesion. The 13 cordotomy cases were the only ones of a series of 71 cordotomies that showed this reference of sensation. This selection of material does not indicate the occurrence of the phenomenon in neurological material ; it merely reflects the kind of material studied.

The features of this reference of sensation will now be summarized. The case of thrombosis of the anterior spinal artery will be considered together with the group of cordotomies, unless the case is mentioned specifically.

There are two differences between the reference of sensation as seen in the cordotomy cases and as seen in the case of forelimb amputation. In the cordotomy cases, only those stimuli that set up impulses conveyed by the spino-thalamic tract were referred ; such were pinching or pricking the skin, painful pressure with an algometer, squeezing muscles, causing painful movements of joints, the injection of hypertonic saline, distension of the bladder, contraction of the bladder caused by the injection of carbaminoylcholine, stretching the anus, applying ice to the skin, spraying the skin with ethyl chloride, applying hot water to the skin. In the amputation case, all forms of stimulation gave rise to referred sensation. In the cordotomy cases stimuli were referred only when they were applied to the region of the body that had been rendered largely or totally analgesic ; in the amputation case, stimuli were referred when applied to parts of the body that were fully innervated.

From the histories given above it will be seen that the sensation might be referred to one constant place, or it might be referred in other ways ; and in any one case more than one mode of reference might occur. In those patients in whom there was no constant region to which sensation was always referred, the sensation was either referred to an analogous place on the opposite normally innervated side of the body, or to regions above or below the region rendered analgesic by the cordotomy, on the same side of the body. In some cases the sensation might be felt at the place to which it was referred immediately ; in others there was a gradual spread of sensation from the place stimulated. In the cases where there was a constant region to which stimuli were referred, there might also be a reference elsewhere than to this place. In some cases no cause for the selection of a specific region to which sensations tended to be referred was found ; the actual region showed no pathological change ; and at necropsy no abnormality was found in the local tissues or in the relevant segment of the cord. Sometimes, however, the sensation was referred to the region of girdle pain which often follows the operation of cordotomy. In other cases the sensation was referred to an analogous place on the opposite side of the body to that where the pain had been before the cordotomy. In one case (Case 11) the region to which sensations were referred had some years previously been the seat of a traumatic process, and the reference of stimuli caused the identical pain in the identical place that had been experienced before. Sometimes there were two areas to which sensation could be referred (as in Case 11) ; these were on the two sides of the body, and each area attracted ipsilateral stimuli. When there was a constant area to which sensation was referred, sensations were referred there whether the stimulation was caudal to, cranial to, or across the midline from this area.

The regions from which sensation was referred were not identical with the hypoalgesic or analgesic regions. Reference of sensation was more likely to occur when the region stimulated was close to the place to which it was referred ; similarly, the heavier or more severe the stimulus, the further away from the place of reference could it be applied and still referred. In some cases limits could be determined beyond which reference of sensation could not be induced. No part of the body, however, was found that did not in some patient give rise to this reference. On most occasions the stimulus was

felt as travelling from the place of application towards the place where it was felt; when the stimulus was applied slowly, this slow travelling of the sensation could be appreciated; when it was applied quickly, it might be felt immediately at the place to which it was referred.

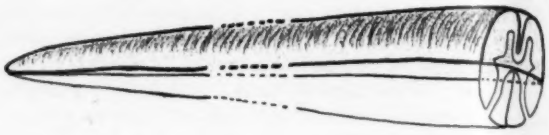
When the region to which sensation was referred was rendered completely analgesic, either by the injection of local anaesthetic solution or by another cordotomy, sensation was no longer referred to this region. An artificial, temporary area of tenderness, induced by the injection of concentrated saline, did not form an area to which sensation was referred. At the place where sensation was felt, the various forms of stimulation mostly caused an identical sensation. But this was not always so: in Case 1 various forms of sensation were experienced, although they were not necessarily those that would be expected from the nature of the stimulus. A further characteristic of the referred sensation was that this sensation was felt as coming from within outwards. Further, the sensation did not have the proper temporal relations of the applied stimulus; it was always felt as prolonged, and it might continue for minutes after the stimulus had been removed; this characteristic resulted in the patient being unable to tell how often or when a new stimulus was applied. The place to which sensation was referred was always within a normally innervated part of the body. Thus in the cordotomy cases it was usually cranial to the hypoalgesic zone; in those cases in which there was a normally innervated region caudal to the analgesic zone, reference might be to this caudal region. When there was no region to which sensation was constantly referred, it was apparent that the distance between the point of stimulation and the place to which it was referred was related to the grade of the stimulus: a slight stimulation would be referred just cranial to the analgesic zone, and a strong stimulation might be referred well into the cervical segments.

This reference of sensation can occur with lesions that divide the spino-thalamic tract in the medulla oblongata; for, although I have had no opportunity of studying the patients, I know of two cases of thrombosis of the posterior inferior spino-cerebellar artery in which it occurred. There is no evidence that it occurs with total division of the spinal cord. The kind of reference of sensation called allochiria has been recorded since Obersteiner's description of it, with lesions of the posterior columns and of the cerebrum; it will not be discussed here.

Discussion

These observations will be discussed in the following way: first, the pathway taken by the impulses subserving the reference of sensation to reach the neurological substratum of consciousness will be considered; secondly, the mechanism of the various features of the reference will be considered; thirdly, these two aspects of the subject will be correlated; and fourthly, other relevant apects of the subject will be discussed.

FIG. 5.—Diagram of caudal end of spinal cord. The stippled region indicates that part of the cord rendered necrotic by the thrombosis of the anterior spinal artery in Case 9.



What pathways do the impulses take to reach the neurological centres of consciousness? Here the case of thrombosis of the anterior spinal artery is particularly important. The extent of the cord rendered necrotic by this vascular occlusion is shown in Fig. 5. It is clear that, at least in this case, the relevant pathways must lie in the posterior half of the cord.

The posterior columns need to be considered as a possible pathway. These columns contain two types of ascending systems: extrinsic fibres, with cells of origin in the posterior root ganglia; and intrinsic fibres with cells of origin in the grey matter of the posterior part of the cord. It is unlikely that the pathway consists of fibres of the extrinsic system. It is unlikely, for the reason that only that part of the sensation subserved by impulses normally conducted by the spino-thalamic tract is referred; the part subserved by impulses normally conducted by posterior column fibres is felt in a normal manner. For instance, when painful pressure with the algometer is referred, the touch and the pressure are felt normally and correctly localized; it is the pain component that is referred. Two different modalities of sensation cannot be subserved by one and the same fibre (as far as is known). Further, it is unlikely, for the reason that such a hypothesis would account for none of the features of the phenomenon, other than the patient's inability to feel pain when the spino-thalamic tract was divided. It would be expected that the pain would be felt in the same place as the touch or the pressure stimulus; there would be no reference of the sensation.

It remains to consider chains of short neurons. This hypothesis is certainly not a new one. In 1899 Münzer and Wiener performed the following experiment in the rabbit and the dog. They carried out complete transverse sections of the spinal cord and also divided the posterior roots bilaterally

between the ganglia and the cord. After waiting for the posterior root fibres to degenerate, they stimulated the relevant area of the posterior columns; and they obtained evidence of typical pain reactions from the animal. The only intact fibres of the posterior columns could be intrinsic fibres. Rothmann (1906) performed a different experiment in the dog. He found that after the lateral, posterior, and anterior columns had been divided at different levels, the dog still manifested evidence of sensibility in the parts of the body from which the known afferent pathways had been removed. He concluded that sensory impulses reach the brain "*via* many short intraspinal tracts" which together form "a conduction chain". Karplus and Kreidl (1914, 1925) proved by carrying out hemisections on opposite sides of the cord of the cat that impulses subserving pain sensibility are conducted not only *via* long tracts but also through the grey matter. As the cats gave evidence of feeling pain immediately after the operation, Karplus and Kreidl were inclined to regard conduction "*via* a chain of short tracts" running within the grey matter as a part of normal conduction. This work was later confirmed by Kletzkin and Spiegel (1952).

As it seems that one may have to postulate a similar conduction of impulses subserving pain sensibility in man, one may ask where such short tracts might lie. Apart from being able to state that some of them are situated in the posterior half of the cord, we have no evidence on which to base an answer to this question. They might be any of the intrinsic fibres of the cord surrounding the grey matter, they might be similar fibres in the posterior columns, they might be fibres of Lissauer's tract, and they might be fibres within the grey matter itself, either within the posterior horn or deeper in the substance of the grey matter.

It is reasonable to suppose that one of the characteristics of conduction *via* chains of short neurons might be the loss of the correct local sign. An inevitable feature of long tract conduction is that the signal is not interfered with on the way; it can be influenced only at the synapses. Indeed, it may be that this insulation from the surroundings is that which enables long tracts to convey local sign. But if the message runs from local station to local station, then at each station it might acquire the local stamp and its original stamp be lost. If the impulses travel along short chains of neurons each group of these might add its own local sign; then the sensation would be felt as passing along the body segment by segment, and felt finally at the segment corresponding to the last group of cells stimulated.

There are other features of conduction along such a chain that might be expected. A long fibre gives out at one end the same number of impulses as it receives at the other. But if there is conduction along chains of neurons, with many synapses on the way, then at each synapse the number of impulses might well be scattered and diminished. Each next link in the chain would then get a diminished input signal; and the end station might well receive an output signal less than the original input. In such a system there might be a tendency for the message to become fainter or even to die out. This form of conduction would then fit in with one of the features of the reference of sensation: a slight stimulation is conducted a short way; stronger stimulation is conducted further.

One more supposition will be made: let us suppose that the short neurons concerned are neurons connecting the cells of origin of the spino-thalamic tract. In such a case it would be expected that the sensation would have a painful character, or the character of heat or cold. But as this short chain type is not the normal mode of conduction, it might also be expected that there would be features other than those found in the normal. It would not be surprising to find that the sensation is felt as though it comes from within, and to find that its quality differs from that to be expected from the nature of the stimulus, and that its quality tends to be the same regardless of the nature of the stimulus. There being chains of neurons connecting the cells of origin of the spino-thalamic tract caudally and to the opposite side of the cord as well as cranially, it would be expected that sensation would be referred caudally and to the opposite side of the body. When the impulses run caudally, they could be conducted to the neurological substratum of consciousness only where there were intact spino-thalamic fibres; in other words, the sensation could be referred caudally only where there was a region of normal or almost normal pain sensibility below the analgesic zone.

Thus the hypothesis of the reference of sensation depending on conduction *via* chains of neurons fits the facts fairly well. It accounts for all the features of the spread and the pattern of the reference; it accounts for the spread across to the analogous place on the opposite side of the body, the spread cranially or caudally to regions supplied by intact spino-thalamic fibres; it accounts for the lack of local sign of that part of the sensation normally subserved by the spino-thalamic tract; it accounts for the fact that the reference is always to a region adequately innervated by the spino-thalamic tract, whether this is cranial, caudal, or on the opposite

side of the body to the place stimulated ; and it also fits in with the fact that the harder the stimulation, the further the sensation is referred, and the less severe the stimulation, the less far it is referred.

It is necessary to consider the mechanism underlying the use of such chains of neurons for the conduction of impulses subserving sensation. The main difficulty is to account for the occurrence of the reference of sensation in some cases of division of the spino-thalamic tracts and not in others. The case of amputation of the forelimb provides a clue. In this case there was no division of an afferent tract. But there was an abnormal state of hyperexcitability in the part of the central nervous system associated with the left upper limb ; this was shown by an actual lowering of threshold, so that stimuli too light to be felt in normal regions were felt here ; and also by the stimuli being felt here for an abnormally prolonged time. It is suggested that the reference of sensation is associated with a state of hyperexcitability of the central nervous system, and that this state may be induced by division of a large number of nerves near the central nervous system or division of an algesic tract inside the central nervous system.

A state of hyperexcitability would cause a reduction of resistance at synapses ; and this lowering of the normal resistance might well allow impulses to overflow into subsidiary pathways. It is possible that under normal conditions the great majority of impulses run along the usual tracts and that a small minority run in these subsidiary pathways ; or it is equally possible that under normal conditions no impulses travel via such subsidiary pathways, all the impulses subserving the various sensory modalities travelling in the posterior columns and spino-thalamic tracts. It is suggested that in the cordotomy cases, where the reference of sensation occurs, the surgical lesion in the spinal cord sets up a state of hyperexcitability. In a sense, a lesion in the cord might be viewed as a switching mechanism, changing the course of impulses, so that they are directed entirely into subsidiary pathways. Why such a state of hyperexcitability should occur in some cases and not in others remains unexplained.

Let us now consider those cases in which there is a constant region (or regions) to which sensation tends to be referred. It can only be conjectured why there is such a region in some cases. For the parts of the body to which sensation was referred were examined after death and no pathological changes were seen and nothing abnormal was found in most cases in the relevant segment or posterior roots. It would seem to be a reasonable hypothesis to believe that in certain regions of the cord groups of cells have got into a persisting state of hyperexcitability with a lowered threshold, that some change has occurred facilitating local synaptic transmission. In some cases one cannot say why such a persisting state would have developed ; but in others, causes can be suggested. When a cancer has been invading some peripheral nerves for months, causing continuous discharge of impulses into one or two segments of the cord, one might imagine that all groups of these segments would become hyperexcitable. If the division of the spino-thalamic tract is incomplete, the structures with a nerve supply from these segments might remain somewhat painful and tender. Case 8 forms an example of reference to the previously very painful and later slightly painful area. If the division of the tract is complete, then the sensation is referred to the same segment, but on the opposite side of the body. The operation of cordotomy causes an area of pain and tenderness cranial to the level of hypoalgesia ; this region would seem to be associated with a local state of hyperexcitability. The total lesion of the brachial plexus in the amputation case seemed to have set up a local area of hyperexcitability on the left side of the chest at that place where the cervical distribution meets the thoracic distribution. And finally there is the intriguing case where there had formerly been an injury to the knee. It will be remembered that this patient had years before broken the right patella, that she had had much pain at that time and that the pain had been taken away by removal of the patella ; the knee had become painless and the patient had forgotten the whole matter. Yet many years later it was brought vividly to her mind by her experiencing the identical pain in the identical place when hot, cold, or painful stimuli were applied to that side of the body. One has to conclude that such a damaged and previously painful structure sets up a kind of *locus minoris resistentiae* in the central nervous system ; further that such a state can persist unnoticed and causing no obvious effects for years ; and that its presence can be shown up by the state of hyperexcitability caused by an operation on the tracts of the spinal cord. Impulses passing this region of the cord under normal conditions do not stimulate it ; but impulses passing it during a state of hyperexcitability or impulses taking abnormal pathways do stimulate it.

Such a region of local hyperexcitability would be envisaged as firing off impulses into neighbouring neurons, some of which would reach the neurological substratum of consciousness whenever a certain threshold is exceeded. It would be exceeded whenever the stimulating effect of impulses arriving

within a certain effective period of time mounted up, or it might be exceeded spontaneously, there being enough local excitation to fire off the group of neurons. In the former case the region of the body supplied by these neurons would be painful all the time. In the latter case the region supplied might be tender or painful when a further aggregate of impulses were added from stimulating the local peripheral nerves and end-organs, or painful when a further aggregate of impulses were added from stimulating distant but connected regions. The impulses set up in these distant regions would have to pour into this hyperexcitable region, and not by-pass it, as occurs with normal long tract conduction. If the total number of impulses within a certain period of time at such a region of hyperexcitability were to be reduced, for example, by removing those arriving from local peripheral nerves (by means of a local anaesthetic block), then there might well be an insufficient accumulation of local stimulation to fire off the group of neurons ; in this case an additional quantity of impulses being poured into the region, originating from stimulation of the body elsewhere, might not be enough to bring the total quantity up to its firing-off threshold ; and then the sensation would not be referred to the region supplied by the hyperexcitable neurons. On the other hand, the region might be spontaneously so hyperexcitable that, in spite of cutting off the impulses arriving from local peripheral nerves, it would still fire off when impulses reached it from distant regions. When a fresh group of impulses arrive at such a region of hyperexcitability, it seems likely that they would increase the local excitability of the region for some time. In this way, one stimulus referred to the place of hyperexcitability would cause sensation going on for some time ; and a subsequent stimulus within that time might cause no new sensation. Such facts were observed.

If there are such groups of neurons in a hyperexcitable state liable to be fired off by passing impulses, why are they not fired off in the normal by impulses travelling along normal long tracts ? The answer, partly, might be that the normal tracts by-pass such groups of neurons. But when conduction is *via* short chains connecting the cells or origin of the spino-thalamic tract, when the pathway does not by-pass this region but runs right into it, the additional number of impulses would swell the local number sufficiently to fire off the region, giving rise to a signal along the spino-thalamic tract, having the local sign of that region. The other part of the answer to this question might be that such an area is fired off by passing impulses in normal tracts in some cases ; such a case would be that of the painful amputation.

Where there is no such region of local hyperexcitability, then it seems likely that the impulses pass along the cord, from synapse to synapse, without firing off any one area in a massive way. In such a case reference of sensation is not to one constant region, but is to an analogous place on the opposite side of the body, or cranially, or caudally, or generally spreading diffusely from the point of stimulation.

Support for these hypotheses comes from experiments on animals. As has been mentioned above, in 1892 Mott observed the condition in monkeys, and in 1913 Dusser de Barenne made an experimental study of it in dogs. There is an outstanding difference, however, between the reference of sensation in the cases of cordotomy and that produced by hemisections of the cord in dogs, cats, and monkeys : in man the reference was from the side of the body contralateral to the incision (the analgesic side) to the ipsilateral side (the normally innervated side) ; whereas in the animals it was from the side of the body ipsilateral to the hemisection to the contralateral side of the body. However, this may not be such an important difference as it seems ; for there is a main difference in the functional anatomy of the algesic pathway in man and in these species : in man this pathway is totally crossed ; in these species it is not so. In the monkeys with a hemisected cord Mott found that " tested by heat, pricking and stimulation by faradism, it was very difficult to decide . . . whether the animal felt better on the side of the section or on the opposite side ". He concluded that there is more sensory loss on the hemisected side than on the opposite side. With regard to the modalities of pain and thermal sense, it is clear that in the monkey and the dog a hemisection does not cause much loss on either side ; it seems that in these species the spino-thalamic tract is more uncrossed than crossed. In comparing the reference of sensation observed by Mott in the monkey and that observed here in man, it seems then justified to neglect the relation of the reference to the side of the cord incised and to turn our attention entirely to the side of the body rendered analgesic or severely hypoalgesic. We then see that in man the sensation was referred from the analgesic side to the opposite side of the body (or elsewhere), and that in Mott's monkeys it was also referred from the most hypoalgesic side to the opposite side of the body. It is to be noted too that Mott found this reference of sensation in three out of nine monkeys operated upon, and that I found it in a minority of patients after cordotomy.

Dusser de Barenne (1913a) came across this phenomenon when he was studying the effect of strychnine on the spinal cord. He knew that the

application of this substance to the dorsal region of one segment of one half of the spinal cord of the dog causes all forms of stimulation of the relevant segment to be felt as apparently painful. He then found that if he performed a hemisection of the cord a few segments cranial to the segment where he put the strychnine, he got paraesthesiae and hyperalgesia on the side opposite to the incision and the site of application of the strychnine. He made no mention of whether he ever found the phenomenon occurring without strychnine being applied. It is clear, however, that he obtained it in all cases in which strychnine was applied. He later (1913b) reported a further experiment on the phenomenon. On this occasion, in operating on a cat, he did not carry out a complete hemisection, but spared the posterior columns. He stated that the phenomenon could be obtained when the lesion was slightly more or slightly less than a hemisection, and he considered that all that was necessary with regard to the extent of the lesion was that it should divide unilaterally a cerebropetal sensory tract, and probably the algesic tract in particular.

Thus the hypothesis of a local region of hyperexcitability gains support from Dusser de Barenne's experimental production of a similar condition; for he invariably produced the condition when he rendered the posterior root entry zone hyperexcitable.

Finally, it remains to observe that there is a practical everyday aspect of this phenomenon. The operation of antero-lateral cordotomy is a disappointing one. It is probable that the phenomenon described above is one of the causes of failure of such pain-relieving operations on the cord. The artificial stimulation applied to the body by deep pressure with the algometer or spraying with ethyl chloride serves to make manifest the stimulation that is acting all the time: stimulation from the invasion of nerve fibrils by cancer, the various stimuli acting spontaneously and intermittently, such as a full bladder, pressure of the weight of the body on a certain analgesic part of the body, a painless bedsore. The sensation from such stimulation may well be referred; in unilateral cordotomies it might be referred to an analogous place on the opposite side of the body or to the same part of the body as that where the pain was originally situated, but on the opposite side of the body; in bilateral cordotomies, it might be referred vaguely upwards, or, where there is "sacral sparing" downwards to the region of normal or diminished pain sensibility, or it might be referred to a certain region outside the analgesic zone, a region which in itself is not pathological and which may or may not be tender, or it might be referred to the zone of girdle pain and tenderness which so often surmounts the zone of hypoalgesia, making this girdle pain continue for weeks or months. It may well be that it is this mechanism of local hyperexcitability and reference of sensation that accounts for the fact so often observed immediately after a unilateral cordotomy—the presence of the pain on the side of the body opposite to the analgesic side, felt in an analogous place. For I have always paid particular attention to the laterality of the pain before the operation, and have pressed the patients to admit that they have had some pain on the unaffected side; only when they have vigorously denied any trace of such pain have we carried out unilateral cordotomies. And yet we have seen an immediate transference of the pain to this normal side after the unilateral operation. This has occurred just as frequently among those who before the operation denied any trace of pain on the normal side as among those who admitted that occasionally they had felt a slight ache running across to the normal side.

Summary

A form of reference of sensation is described. Although most of the examples of the syndrome occur after division, either surgical or natural, of the spino-thalamic tract or tracts, it may also occur without any lesion of the long tracts.

The mechanism and relevant anatomical considerations are discussed.

I wish to thank Dr. E. A. Carmichael for his helpful criticism, Mr. Wylie McKissock, who operated on Cases 39, 11, 32, and who allowed me to investigate Case 62, Mr. Murray Falconer, who operated on Cases 54 and 40, Mr. Bernard Harries, who operated on Case 41, and Dr. A. Barham Carter who allowed me to investigate Case 9.

Cases 39, 11, 32, 38, and 62 were in the National Hospital; their hospital case numbers are respectively 14334, 23011, 29786, 36799, and 58071.

References

Dusser de Barenne, J. G. (1913a). *Folia neuro-biol., Lpz.*, 7, 549.
——(1913b). *Mschr. Psychiat. Neurol.*, **34**, 523.
Karplus, J. P., and Kreidl, A. (1914). *Pflügers Arch. ges. Physiol.*, **158**, 275.
——, ——(1925). *Ibid.*, **207**, 134.
Kletzkin, M., and Spiegel, E. A. (1952). *Fed. Proc.*, **11**, 83.
Mott, F. W. (1892). *Philos. Trans., B.*, **183**, 1.
Münzer, E., and Wiener, H. (1899). *Neurol. Zbl.*, **18**, 962.
Obersteiner, H. (1881). *Brain*, **4**, 153.
Ray, B. S., and Wolff, H. G. (1945). *Arch. Neurol. Psychiat., (Chicago)*, **53**, 257.
Rothmann, M. (1906). *Berl. klin. Wschr.*, **43**, 47, 76.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 101.

AWARENESS OF BLADDER FILLING WITH DIVIDED SENSORY TRACT

BY

P. W. NATHAN

From the Neurological Research Unit of the Medical Research Council, the National Hospital, Queen Square, London

It takes a baby at least two years to learn to interpret certain sensations as indicating that the bladder needs to be emptied. When the afferent pathway from the bladder in the spino-thalamic tract has been divided, these specific sensations are no longer experienced. However, when this pathway from the bladder has been divided and the normal sensation underlying the desire to micturate has thereby been removed, it is surprising to find that many patients experience other sensations related to bladder filling and emptying ; and they can learn to interpret such sensations, which intrinsically do not feel as though they are related to the desire to micturate, as an indication that the bladder needs to be emptied. The purpose of this paper is to describe and draw attention to the more common of these sensations, to report an investigation of its mechanism, and to present evidence on the pathway by which the impulses subserving it reach the central nervous system.

In patients with total division of the spinal cord the occurrence of a poorly localized abdominal sensation indicating a full bladder has been reported by Bálint and Benedict (1906), Riddoch (1921), Denny-Brown and Robertson (1933), Voris and Landes (1940), Donovan (1947), and Kuhn (1950) ; it has been reported in total lesions of the cauda equina by Kocher (1896) and Denny-Brown and Robertson (1933) ; and in patients with division of the lateral part of the spino-thalamic tract Nathan and Smith (1951) recorded the presence of this and other substitute sensations. The cases reported by Kuhn are of particular interest, as he made some observations on the nature of the stimulus that may give rise to the sensation in patients with proved total division of the cord ; reference to his material will be made throughout this study.

The abdominal sensation is not the only sensation that may act as a substitute for the normal sensation underlying the need to micturate. Occasionally, after the spino-thalamic tract has been divided, there are spontaneous tingling paraesthesiae in the lower part of the body ; these may be accentuated when the bladder is full. In some patients there may be reference of sensation from below the level of the surgical lesion to the parts of the body above it; such referred sensations may originate in the bladder. As was previously mentioned by Nathan and Smith (1951), a very full bladder may cause one of the following sensations : a frontal headache, a feeling of being about to shiver or of actual shivering movements, a feeling of a need to take a deep breath ; these are the sensations that accompany the reflex effects described in total cord division by Guttmann and Whitteridge (1947). There are also the sensations arising in the urethra that occur immediately before micturition ; these were also briefly described by Nathan and Smith.

Unless the clinician is aware of the possible existence of these substitute sensations, he may be misled by the answer to the question whether the patient knows when he needs to micturate or not. For patients having these substitute sensations may not explain spontaneously that although they know when they need to empty their bladders they have not acquired this knowledge in the usual way ; it may be necessary to tell them of the existence of the normal sensation of needing to micturate and of this vague abdominal sensation before they will state that this is the sensation which they experience. Further, these sensations are useful, as they can form adequate substitutes for the normal sensation when this is absent.

This vague abdominal sensation was present in 11 of 20 patients who had the operation of bilateral antero-lateral cordotomy ; it was also experienced by one patient with a thrombosis of the anterior spinal artery, causing extensive destruction of the afferent pathway from the bladder.

The Nature of the Sensation

The most common of the substitute sensations related to bladder filling is a vague feeling in the abdomen, poorly localized and difficult to define. All patients say that it is a sensation that they have not previously experienced. Many of them, when

they first experience it, believe that they are distended with wind. One young man described it as follows : " When my belly feels very full, as though I have eaten a lot, then I know I have to empty my bladder." Sometimes the sensation is described as an ache, which may have an unpleasant component, but it is uncomfortable rather than painful. All patients agree that this feeling of abdominal fullness does not seem to be connected with the bladder. It is experience that teaches them to use this non-specific sensation as an indicator of bladder fullness. The sensation is not usually noticed immediately after division of the spino-thalamic tracts ; it may take days or weeks before the patient becomes aware of it.

The Origin of the Sensation

As this sensation comes on when the bladder is full and goes after the bladder has been emptied, it is reasonable to look for its source in the bladder. However, certain observations were made that showed that the bladder could not be the only source of the sensation. Accordingly the following four possible sources of the nervous inpulses giving rise to the sensation were examined : the bladder ; an increase in intra-abdominal pressure ; the pelvic floor ; and the rectum.

Cases will now be presented as illustrations of the evidence concerning these four possible sources of the sensation.

The Bladder.—It seems to be that any inflow into the central nervous system of impulses from the bladder may give rise to this sensation. Undoubtedly the impulses consequent on stretching and contracting of the bladder muscle fibres form one main source of the sensation.

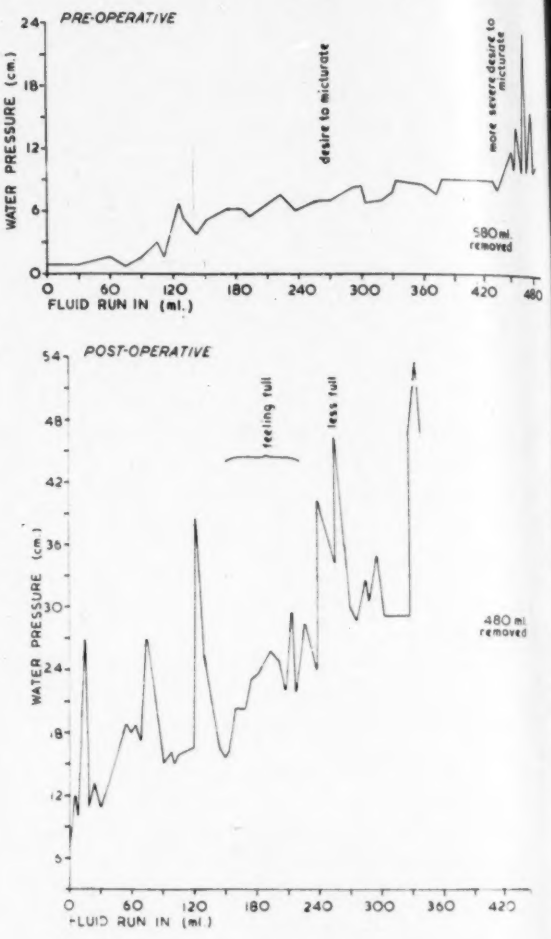
An increase in bladder pressure, as occurs during the performance of cystometrography and cystoscopy, has on innumerable occasions given rise to the sensation. This sensation, however, is not so closely related to changes in bladder pressure as is that occurring in the healthy subject interpreted as the need to micturate. It may not become more intense with sudden increases of bladder pressure and may take several minutes to disappear after the bladder has been emptied.

The nature of the sensation and its rather vague relation to the changing bladder pressure is well illustrated by the following case.

Case 10*.—This young man had an extensive sarcoma of the left innominate bone ; for the pain from this condition, a bilateral cordotomy was performed. A cystometrogram carried out before the operation

* The numbers of the cases are the same throughout this and all other papers by Nathan and Smith.

FIGS. 1a and 1b.—Pre- and post-operative cystometrograms.



(Fig. 1a) was normal ; the bladder had a large capacity but one within the range of the normal.

Following operation there was analgesia throughout the right side of the body below the eleventh thoracic and throughout the left side below the tenth thoracic dermatome. The patient had retention of urine, no desire to micturate, and no pain when the bladder was allowed to become very distended immediately after the operation. He soon found, however, that he could tell when his bladder was full as he got a sensation of fullness. This was vague and seemed to be generally within the abdomen ; it was the same as the feeling of being distended with wind ; it was by experience that he learnt that it indicated that his bladder needed emptying.

A cystometrogram was carried out six weeks after the operation (Fig. 1b). The shape of the curve does not concern us here. No sensation of a normal kind occurred either with the gradual filling of the bladder or with the large spontaneous contractions. The words " feeling full " refer to the vague sensation of abdominal fullness ; it was experienced when 200 ml. of fluid had been run into the bladder ; such an amount of fluid could not have

over-distended the bladder. It will also be seen from this figure that the sensation diminished as the filling and the pressure of the bladder increased.

From this typical case it can be concluded that slowly filling the bladder in a normal manner induces the abdominal sensation. It is also seen that the sensation is not proportional to the amount of fluid in the bladder or to the amount of reflex contraction of the bladder. These points are shown more clearly in the next case.

Case 9.—This patient developed a thrombosis of the anterior spinal artery during the second stage of an abdominal sympathectomy. Analgesia resulted throughout the body below the second lumbar dermatome. The bladder had minimal tone, manifested no spontaneous contractions and failed to respond to stretch by an increase in pressure.

When the bladder was washed out, although the pressure was not allowed to rise above 7 cm. of water, the patient experienced the sensation of abdominal distension ; and the sensation, once aroused in this way, would always continue for many minutes after the lavage had ceased and the bladder had been emptied.

To observe how the character of the vague sensation might change as the bladder became over-distended, the patient was left for 12 hours without being catheterized. She had no distress, no pain, and no normal sensation of needing to micturate. She got " a vague feeling of fullness, a discomfort, not a pain " situated somewhere in the abdomen between the umbilicus and the pubis ; this sensation did not become more intense or painful with the increasing distension.

From many observations made during cystometrography and cystoscopy in the 12 patients, it has been concluded that this abdominal sensation may arise from normal physiological stretching of the bladder. This conclusion was from the outset to have been expected, although the sensation does not feel to the patient as though it is connected with the bladder.

However, it may be surprising to realize that this same abdominal sensation may be experienced after the bladder has been removed. The presence of this substitute sensation in a patient without a bladder is illustrated by the following case.

Case 60.—A man with a carcinoma of the bladder was operated upon by Mr. David Wallace, who performed the following ingenious operation. He carried out a total cystectomy, dividing the urethra through its prostatic part ; he then mobilized a piece of ileum, transplanted the ureters into it, and joined the loop of ileum to the divided urethra. Thus the patient was provided with a new bladder.

Two to three weeks after the operation, the patient found that he knew when his artificial bladder was becoming full, as he experienced " a blown-up feeling " in the lower abdomen. This sensation was not painful ; it was not the sensation of colic of the bowel ; and it was not the sensation of wind, " because wind hurts ".

Thus this patient experienced a substitute abdominal sensation which he came to interpret as indicative of bladder fullness, although the actual bladder had been completely removed. It is to be emphasized that, as far as one can judge from verbal descriptions by patients, this sensation originating elsewhere than the bladder was the same as that originating in the bladder.

Although it has been concluded that the sensation may originate in the bladder, it may also originate from sources other than the bladder.

An Increase in Intra-abdominal Pressure.—There is no doubt that the sensation may be aroused by an increase of the intra-abdominal pressure ; and there is also no doubt that it does not invariably so arise. The role of an increase in the intra-abdominal pressure in increasing the sensation is illustrated by the following case.

Case 19.—This man had a bilateral cordotomy for the pain caused by a carcinoma of the bronchus. Following the operation there was complete analgesia throughout the body below the fourth thoracic dermatome.

Ten weeks after the operation, the bladder was filled through a catheter. When spontaneous contractions occurred, the patient had a substitute sensation in the form of pricking in the neighbourhood of the pubis and in the lower abdomen ; this sensation would continue for minutes after the pressure was reduced by lowering the reservoir of fluid. When the patient had this sensation, it could be increased by gentle pressure on the upper abdomen. As this pressure was applied when the bladder was actively contracting, no increase in the intra-vesical pressure occurred, as shown by manometric readings taken during this procedure.

However, it is also clear that the sensation may arise without there being an increase in intra-abdominal pressure. On many occasions patients who were subject to this sensation were induced to strain as though defaecating or as though trying to expel urine ; such a manoeuvre increased the intra-abdominal pressure, but did not induce this abdominal sensation.

It is also clear that when the sensation arises in the bladder, this is not due to a concomitant rise in intra-abdominal pressure. For instance, the sensation sometimes occurred when only 200 to 300 ml. of urine was in the bladder and when the bladder was contracting firmly ; such small amounts of fluid in the bladder could not cause a rise in the intra-abdominal pressure.

Further evidence that the sensation may arise without any increase in the intra-abdominal pressure is provided by the cases of total transection of the spinal cord, published by Kuhn. In four patients

(D.La., J.D., J.B., and McC.), Kuhn obtained the feeling of fullness in the lower abdomen or a tightening in this region or aching below the umbilicus when he stretched the anal sphincter. As this stretching is not associated with an increase of the intra-abdominal pressure, it follows that the abdominal sensation does not necessarily arise from an increase in the intra-abdominal pressure.

The Pelvic Floor.—That the sensation did not originate from the pelvic floor or the perineal musculature was made clear by the following case.

Case 61.—Mrs. R., before admission, had had an intrathecal injection of alcohol in order to alleviate the pain from a carcinoma of the cervix uteri. This had destroyed all the anterior and posterior roots of the cauda equina. The perineal and pelvic musculature had no tone and could not be contracted voluntarily. The patient was not incontinent of urine ; she could empty the bladder by pressing with the hands on the lower abdomen. She had the substitute sensation so clearly that she always made use of it to empty the bladder.

From this case, it is concluded that the sensation does not originate in the contraction of the muscles of the pelvic floor.

The Rectum.—There is no evidence that the sensation can originate in the rectum. No patient experiencing the sensation has lost it after a full rectum was emptied. In many patients the sensation disappeared on emptying the bladder, though the rectum remained full of hard masses of faecal material.

To investigate further the rectum as a possible source of the sensation, a balloon was passed into the rectum of several patients and then distended. Though the patients usually became aware of a sensation of distension of the rectum, it was quite unlike the vague abdominal sensation under consideration. Finally, four patients who previously had the rectum excised experienced the substitute sensation ; in them, the sensation could not have arisen in the rectum.

Thus an enquiry into the origin of this abdominal sensation shows that it can originate in the bladder, and/or from an increase in intra-abdominal pressure while the bladder pressure remains constant. There is no evidence that it originates in the floor of the pelvis or the rectum.

The Pathway of Impulses Subserving the Sensation

It has been shown by Nathan and Smith (1951) that after the afferent pathway from the bladder in the spino-thalamic tract has been divided this abdominal sensation may be experienced. The possible remaining pathways which may subserve this substitute sensation will now be considered, first when it arises from the bladder, and secondly when it arises from an increase in intra-abdominal pressure.

The Pathway from the Bladder.—Two possible routes must be considered : first, a pathway within the spinal cord, and secondly, one outside the cord. The route outside the cord would be afferent nerves running in company with the sympathetic nerves and chains ; these nerves would eventually reach the spinal cord via the posterior roots in the upper thoracic region.

Observations reported by Kuhn (1950) and by Beck (1949) on patients with total transections of the cord make it clear that there are afferent fibres subserving sensation within the sympathetic chain. In Kuhn's patients with division of the cord, the only possible afferent pathway from the pelvic structures to the upper spinal cord was that running with the sympathetic nerves and chain. In his patients, the impulses giving rise to the sensation under discussion must have made use of this pathway. Further evidence for conduction *via* a pathway incorporated in the sympathetic chain comes from the well studied case reported by Beck. In this case the division of the cord had been confirmed at operation : " Immediately below the third thoracic segment there is division of the cord. There is a defect of 2 cm. between both ends of the cord ". The bullet that had divided the cord had also divided the sympathetic chain on the right and had destroyed the right fourth thoracic sympathetic ganglion. This patient, " shortly before micturition ", which occurred reflexly when 200 to 300 ml. of urine was in the bladder, experienced " a feeling of cramp in the neighbourhood of the bladder, which always slowly ascended along the left side of the trunk. It went away after micturition ". The fact that the sensation was felt mounting up the left side and that the right sympathetic chain had been divided may suggest that the pathway being used in this case was one running along the left sympathetic chain.

It thus appears that there are afferent nerves running with the sympathetic system which conduct impulses subserving sensation from pelvic structures, and that the sensory function of these nerves becomes manifest when the spinal cord has been totally divided at a level caudal to the entry of the fibres accompanying the sympathetic chain. Further, as there was a proved total division of the cord immediately below the third thoracic segment in Beck's case and at the fourth thoracic segment in Kuhn's case McC., it seems that these afferent nerves must reach the spinal cord at a level cranial to the fourth thoracic segment. Thus in those patients with a total division of the cord, the afferent

pathway for the impulses subserving this abdominal sensation must be *via* the fibres accompanying the sympathetic system. In the patients investigated here, those in whom the spino-thalamic tracts had been divided, it is probable that the same sensation was subserved by the same pathway ; it is possible, however, that in these patients the pathway was via the sacral posterior roots and the posterior columns of the cord.

The Pathway when the Sensation Arises from an Increase in Intra-abdominal Pressure.—When the sensation arises from an increase in the intra-abdominal pressure, the relevant impulses may travel *via* afferent nerves accompanying the sympathetic system, or, in some cases, they may travel *via* the posterior roots and then the posterior columns. There are, however, two other possible pathways to consider : the branches of the phrenic nerve supplying the abdominal surface of the diaphragm and the peritoneum covering it, and the coeliac branches of the vagus. It would seem to be unlikely that the phrenic nerve is used as a pathway, for no case was seen in which a sensation was felt in the shoulder-tip ; if the phrenic nerve-endings were being stimulated, it is likely that the sensation would be referred to this territory.

It has not been possible to obtain evidence as to which pathway is used ; for in those patients in whom the sensation could be shown to occur in association with a rise in intra-abdominal pressure, the branches of the vagus, many sympathetic fibres, and the posterior columns were intact.

Summary

A sensation is described which occurs after the normal afferent pathways from the bladder have been divided. Patients may learn to use this sensation as a substitute for the normal sensation giving rise to the desire to micturate.

The possible sources of this sensation have been investigated. It is concluded that the impulses subserving it may originate in the bladder and/or from an increase in intra-abdominal pressure.

When the cord is totally divided, the impulses subserving this sensation are conducted *via* afferent nerves accompanying the sympathetic nerves ; it is shown that some of these nerves enter the spinal cord at a level cranial to the fourth thoracic segment. When only the spino-thalamic tracts are divided, the impulses may follow the same path, or they may run in the posterior columns. When the sensation originates from an increase in intra-abdominal pressure, it is possible that the coeliac branches of the vagus also conduct the relevant impulses.

I wish to thank Dr. E. A. Carmichael for his helpful interest, Mr. Wylie McKissock for his continuous enthusiastic cooperation, and Mr. O'Connell, Mr. David Wallace, and Dr. Alan Barham-Carter, who were so kind as to allow me to investigate their cases.

References

Bálint, R., and Benedict, H. (1906). *Dtsch. Z. Nervenheilk.*, **30**, 1.
Beck, K. (1949). *Ibid.*, **160**, 55.
Denny-Brown, D., and Robertson, E. G. (1933). *Brain*, **56**, 149.
Donovan, H. (1947). *Lancet*, **1**, 515.
Guttmann, L., and Whitteridge, D. (1947). *Brain*, **70**, 361.
Kocher, T. (1896). *Mitt. Grenzgeb. Med. Chir.*, **1**, 415.
Kuhn, R. A. (1950). *Brain*, **73**, 1.
Nathan, P. W., and Smith, M. C. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 262.
Riddoch, R. (1921). *J. Physiol., Lond.*, **54**, 134.
Voris, H. C., and Landes, H. E. (1940). *Arch. Neurol. Psychiat., (Chicago)*, **44**, 118.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 106.

TWO CASES OF MYOPATHY LIMITED TO THE QUADRICEPS

BY

JOHN N. WALTON

From the Department of Medicine, King's College, University of Durham, and the Royal Victoria Infirmary, Newcastle upon Tyne

Bramwell, in 1922, demonstrated before the Royal Society of Medicine two cases suffering from a form of myopathy which appeared to be limited to the quadriceps. A third similar case was reported by Denny-Brown in 1939, but no subsequent descriptions of this condition have appeared in the literature. All of the three patients previously reported were over 40 years of age; this paper describes two further cases of this type, one in a young man.

Case Reports

Case 1.—J. O., a salesman aged 22 years, in March, 1951, four weeks after joining the Army, found great difficulty in doing physical training; his thighs seemed to stiffen and to slow him down. At the same time he noted considerable difficulty in rising from the floor or from the crouching position, and had to make use of his arms. After exercise he found it difficult to climb stairs, but after rest this was less noticeable. His previous health had been good; his parents and three sisters were healthy and there was no family history of muscular disease.

On examination on August 17, 1951, he was a healthy looking soldier: he walked with a normal gait, but on rising from the floor or from a crouching position he was compelled to use his arms. The cranial musculature, the upper limbs, and the trunk showed no abnormality; there was no myotonia. In the lower limbs there was striking hypertrophy of the lateral vasti (similar to that seen in Case 2, see Fig. 2), but the medial vasti were atrophic. There was marked weakness of extension of the knee joint and of adduction of the thighs. Although the left calf was somewhat larger than the right, and the circumference of the left leg at mid-calf was ½ in. greater than the right, the muscles below the knee were otherwise normal in appearance and power. All the tendon reflexes were active and equal on the two sides.

On April 3, 1952, the patient was admitted to the Royal Victoria Infirmary under the care of Professor F. J. Nattrass. His clinical condition was unchanged; an intramuscular injection of 1·25 mg. of prostigmine produced no subjective or objective change in his condition. An electromyogram from the right vastus lateralis and from the left vastus medialis was recorded with concentric needle electrodes. The pattern was similar in the two sites; there was no spontaneous activity but on volition the motor units were profuse, reduced in amplitude, and polyphasic; frequency analysis (Walton, 1952) revealed a shift to the right.

A muscle biopsy was taken from the right vastus medialis; it showed that many muscle fibres were severely atrophied while others were enlarged to more than 100 μ in diameter and showed central migration of sarcolemmal nuclei (Fig. 1). There was some fatty infiltration and replacement fibrosis; no necrotic change in muscle fibres, cellular infiltration, or regenerative activity was seen. Sections of a biopsy specimen from the vastus lateralis showed a considerable

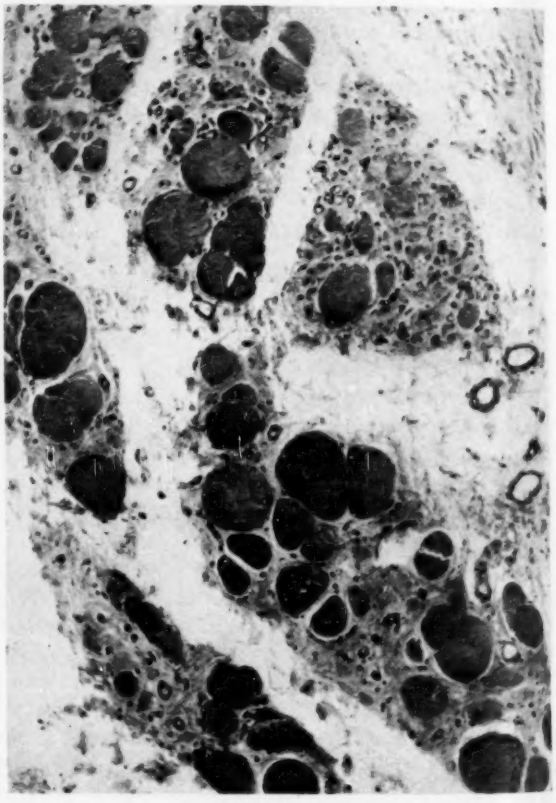


FIG. 1.—Transverse section from the vastus medialis (haemalum and eosin, × 100). Many muscle fibres are atrophic, others are enlarged, rounded, and show central migration of sarcolemmal nuclei. There is some fatty infiltration and replacement fibrosis.

infiltration with fat. Many of the muscle fibres appeared healthy, many others were enlarged and showed central sarcolemmal nuclei ; only a few were atrophic.

The patient was discharged from hospital and received 150 mg. α-tocopherol daily. On November 7, 1952, he was subjectively improved and no longer noted stiffness in the thighs although he still experienced difficulty in climbing stairs towards the end of the day. There was no objective change in his condition and the α-tocopherol was discontinued. He was seen again in April, 1953, and was again unchanged. In February, 1955, his symptoms remained slight ; he walked six or seven miles daily and had clearly shown no deterioration. The hypertrophy of the lateral vasti was still very marked and was more evident on the right side ; both adductor groups and medial vasti were atrophic and weak. The right knee jerk was active, the left depressed.

Case 2.—W. A., a railway shunter, was aged 57. In 1946, at the age of 48, he noted some weakness of the left leg ; the knee tended to give way easily and he fell on two or three occasions. An orthopaedic surgeon could find no abnormality in the knee joint. During the succeeding months the knee tended to give way more frequently and similar, though less severe, weakness was noted on the right side. He began to have difficulty in climbing stairs and after bending or kneeling for some time he found considerable difficulty in standing up again. For about a year the weakness appeared to become worse, but since that time there had been no further deterioration in his condition. He had been compelled to change his occupation, but was working regularly as an electrician's mate in September, 1951, although the knees continued to give way from time to time. Apart from symptoms of peptic ulcer the patient gave no history of any illnesses of note ; his parents died in old age and had no symptoms of muscle disease, while five brothers and six sisters were well.

FIG. 2.—Photograph of the lower limbs of Case 2. There is striking hypertrophy of the lateral vasti while the medial vasti are atrophic.

On September 20, 1951, the patient was seen to be a healthy looking, vigorous man who walked briskly with a normal gait. He was slow in climbing stairs and made use of his hands on rising from the floor. No abnormality was noted in the cranial musculature, upper limbs, or trunk. The lower limbs showed marked hypertrophy of the lateral vasti and undoubted atrophy of the medial vasti (Fig. 2). There was marked weakness of knee extension and of adduction of the thigh, but abduction was powerful. The muscles below the knee were normal in appearance and power, the knee jerks were moderately depressed, but all other tendon reflexes were active and equal.

An intramuscular injection of 1·25 mg. prostigmine produced no subjective or objective change in the patient's condition. An electromyogram from the right vastus lateralis was recorded with a concentric needle electrode. There was no spontaneous activity ; many areas of the muscle were electrically silent on volition, suggesting fatty infiltration, but in other areas many motor units were polyphasic ; a sustained, complex, low-amplitude interference pattern was obtained, and on frequency analysis there was a shift to the right. Muscle biopsy was refused.

The patient was seen again on November 18, 1952, June 22, 1953, and September 22, 1955, and showed no subjective or objective change. There was no evidence that the myopathic process had spread to involve other muscles.

Discussion

Despite the difference in age, the similarity of the clinical manifestations in these cases suggests that both patients were suffering from a myopathic process, limited to the quadriceps, and producing atrophy of the medial vasti with a remarkable enlargement of the lateral vasti. It is probable that the latter change resulted at least partly from compensatory hypertrophy, even though the electromyographic findings in Case 2 indicated that much of the swelling was due to accumulation of tissue other than muscle. Furthermore, in Case 1, although the vastus lateralis was powerful, a biopsy specimen from this muscle showed early myopathic changes and fatty accumulation. It is of interest that Bramwell (1922) described compensatory hypertrophy of the tensor fasciae latae in one of his cases, while Denny-Brown's (1939) patient showed selective atrophy of the vastus medialis. The mechanism of muscular enlargement in patients

with muscle disease is poorly understood. The fact that the calf muscles of a patient with progressive muscular dystrophy are often characteristically enlarged and that histological examination reveals a massive infiltration with fat has given rise to widespread use of the term pseudohypertrophy. However, this muscle group characteristically remains powerful until a late stage of the disease and it appears that some muscle fibres in such muscles may show true hypertrophy. Certainly in Case 1 of the present report the biopsy specimen from the vastus lateralis showed certain findings which could be interpreted as being due to a combination of compensatory hypertrophy and pseudohypertrophy.

In Denny-Brown's case, histological examination of the affected muscle revealed changes which were characteristic, not of progressive muscular dystrophy, but of "late-life" (Nevin, 1936) or "menopausal" (Shy and McEachern, 1951) muscular dystrophy. Adams, Denny-Brown, and Pearson (1953) and others believe this disorder to be a form of polymyositis, nosologically distinct from true muscular dystrophy. It thus appears that occasionally the polymyositis syndrome may be limited in its clinical effects to the quadriceps. Laurent (1953) has observed a case which may be of this type. A woman of 52 years gave a history of 11 years' progressive weakness and wasting of both quadriceps; she showed a dramatic improvement in power following an intramuscular injection of prostigmine and on continuous oral therapy this improvement was maintained until her death many years later. In this connexion it is of interest that I have observed a variable response to prostigmine in some cases of polymyositis.

So far as the cases in the present report are concerned, however, it is clear from the histological findings that Case 1 was not suffering from polymyositis. In this patient the muscular changes were those which are believed to be characteristic of progressive muscular dystrophy. In the absence of histological evidence it is impossible to be certain as to the nature of the pathological process in Case 2 but the similarity of his symptoms and signs to those of Case 1 was striking. It seems probable that both patients were suffering from a true muscular dystrophy which for some reason was localized to the quadriceps. Probably this disorder may reasonably be regarded as a *forme fruste* of the limb-girdle type of muscular dystrophy, corresponding to the abortive cases of the facioscapulohumeral type, which are much more common (Walton and Nattrass, 1954).

Summary

Two cases are reported of a form of myopathy limited to the quadriceps, in which there was atrophy and weakness of the adductors and medial vasti but enlargement of the lateral vasti.

It is pointed out that certain cases of this type may be found to be suffering from that form of the polymyositic syndrome referred to as "late-life" or "menopausal" muscular dystrophy. Reasons are given, however, for suggesting that the two cases of the present report were examples of a *forme fruste* of limb-girdle muscular dystrophy.

References

Adams, R. D., Denny-Brown, D., and Pearson, C. M. (1953). *Diseases of Muscle*. Hoeber, New York.
Bramwell, E. (1922). *Proc. roy. Soc. Med.* (Sect. Neurol.), **16**, 1.
Denny-Brown, D. (1939). *Ibid.*, **32**, 867.
Laurent, L. P. E. (1953). Personal communication.
Nevin, S. (1936). *Quart. J. Med.*, **5**, 51.
Shy, G. M., and McEachern, D. (1951). *Journal of Neurology, Neurosurgery and Psychiatry.*, **14**, 101.
Walton, J. N. (1952). *Ibid.*, **15**, 219.
——, and Nattrass, F. J. (1954). *Brain*, **77**, 169.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 109.

A STUDY OF 25 CASES OF COMPRESSION OF THE CAUDA EQUINA BY PROLAPSED INTERVERTEBRAL DISCS

BY

W. BRYAN JENNETT

From the Department of Neurological Surgery, Radcliffe Infirmary, Oxford

Most cases of sciatica due to intervertebral disc lesions are in fact partial cauda equina lesions. Commonly they are unilateral and there is muscular weakness, wasting, reflex abnormalities, and sensory impairment referable to compression of one or more roots. These defects are rarely disabling in themselves and are of importance chiefly in diagnosis and localization. In some cases the weakness may amount to complete paralysis of the anterior tibial group of muscles and a drop foot results. In a smaller number there are profound bilateral signs: total distal paralysis of the lower limbs, sensory loss in the whole sacral distribution, and sphincter paralysis. This is one type of lumbar disc lesion which does not respond to conservative treatment, and it is the only type which may constitute a threat to life. It is remarkable that it has not figured more prominently in the vast literature which has accumulated since Mixter and Barr (1934) " discovered " the intervertebral disc lesion 22 years ago.

The largest number reported together is eight, described by Ver Brugghen (1945) with one fatal but unverified case. There are other isolated cases in the literature of which I have collected 34 with verified lesions and with sufficient data to make some useful comparisons with the present series. (Dandy, 1929 and 1942; Eyre-Brook, 1952; French and Payne, 1944; Kaplan and Umansky, 1951; Kennedy, Hyde, and Kaufman, 1948; Nicaud, 1947; O'Connell, 1944; Rouqués, David, and Pautrat, 1948; Schneider, 1949). This paper reports a further 25 verified cases, which were treated in the Radcliffe Infirmary and associated hospitals in Oxford between 1937 and 1955, during which time about 1,000 cases of lumbar disc lesion were verified at operation. Although the incidence is thus about 2% in the surgical material (similar to that found by Ver Brugghen), the actual incidence of cauda equina paralysis in all lumbar disc lesions is clearly not so high because almost all cases of cauda equina compression are operated on, whereas only a small proportion of cases of sciatic pain presumed to be due to disc lesions are dealt with surgically and so verified.

Paralysis of the cauda equina may be the first significant manifestation of a lumbar disc lesion, although more commonly it is a sudden complication of an attack of " ordinary " sciatica, either an initial attack or one of a series of recurrent attacks. Two types of lesion have been encountered. In the first there is a massive protrusion of the disc which takes up all the available room in the vertebral canal and behaves much like a large extrathecal tumour. In other cases the disc protrusion is smaller, by no means large enough to fill the vertebral canal or crush the cauda equina and often of the type seen in cases of uncomplicated sciatica, but it is associated with a well demarcated band of dense adhesions within the theca which strangle the roots of the cauda equina.

Case 1.—A. H., a man, aged 56 (R.I. 7352/40), 20 years before admission had an attack of backache and left-sided sciatica for two weeks. In the 18 months before admission he had three or four attacks of right-sided sciatica with backache, and four months before admission an attack proceeded to bilateral sciatica. The morning after this he woke with complete double sphincter paralysis and the right leg useless and numb. He had developed decubitus ulcers on one buttock and both heels two to three weeks before admission.

On arrival he was toxic, pyrexial, and hiccoughing, the blood urea being 140 mg./100 ml. He could not move the right leg against gravity whilst paralysis was complete below the knee; there was distal weakness and wasting in the left leg. Sensory loss was asymmetrical, involving the saddle area and on the right L.4 and L.5 dermatomes as well. The ankle jerks were absent and he had retention of urine (with infection) and a patulous anal sphincter. The C.S.F. protein was 600 mg./100 ml. and the fluid was xanthochromic; myelography showed a block at L.2–3 interspace.

The patient died of uraemia a fortnight after admission without having been operated on, and at necropsy a small disc protrusion was found compressing the right third lumbar root. This lesion appeared to be too small to have accounted for the paralysis, but on opening the theca there was found to be a dense and sharply de-

marcated band of arachnoid adhesions exactly opposite the disc protrusion. This band was lightly adherent to the inner aspect of the dura, but the roots of the cauda equina were firmly embedded in it and could only be isolated by sharp dissection. Above and below this band the leptomeninx appeared to be normal.

This type of lesion, which is less common than the massive prolapse, is also seen in association with disc lesions in other parts of the vertebral canal, for example, in the cervical region where some authors regard it as important in the myelopathy associated with cervical spondylosis. Pathologically, it may be thought of as a " friction arachnoiditis ", and, although a chronic process, paralytic symptoms may develop just as suddenly as when a massive protrusion is present (Stookey, 1927). The primary pathological process, the protrusion of the disc into the vertebral canal, must be similar to that in ordinary sciatica but differing in some cases in size and in some in the tendency for adhesions to develop around the nerve roots within the theca. This study was undertaken to see whether any reason could be found for some cases behaving in this serious manner, whether any steps could be taken to prevent it, and what the results of treatment were. It will be seen that the first two objectives have succeeded only to a very limited extent. It will also be seen that the term " compression " is used as a convenient description of the syndrome, although not all the cases were subject to actual compression by a massive protrusion.

Analysis of Cases

Fifteen of the patients were men, 10 were women, The youngest was 20 years old, the eldest 72, and the remainder about equally distributed between the fourth, fifth, and sixth decades. Compression of the cauda equina thus occurs rather later than the uncomplicated sciatic pain which usually leads a patient to seek advice for a disc lesion.

In 14 cases there was a history of repeated attacks of backache and sciatica for many years. There was nothing very unusual about these attacks, although in two cases the sciatic pain had been bilateral and in two others it had alternated between the two sides. In most cases the final attack began just as the previous ones had done, although it usually developed into the most painful attack yet experienced. In one case the paralysis occurred four years after an operation for a disc protrusion at the same level.

In 11 cases the cauda equina symptoms occurred in the first attack. In one case there had been continuous back pain and sciatica for 12 months before the onset of cauda equina paralysis, but usually it was a much shorter period, the shortest being three weeks. In two patients in this group the lesion was related to pregnancy and the puerperium; in one, back pain and sciatica began in the fourth month of pregnancy and were followed a month later by symptoms of cauda equina compression; in the other, back pain and sciatica began in the third week of the puerperium and were followed two months later by compression symptoms. O'Connell (1944) described four cases in the puerperium.

In 12 cases the onset of compression was sudden; in the remainder it was rapid, complete paralysis developing over a few days. In these latter cases the march of events simulated inflammatory lesions such as epidural abscess or even a rapidly growing tumour.

When the onset is sudden, it might be expected that it would be attributed to some sudden movement, strain, or other injury but that was so in only three cases, whilst in four other cases, by contrast, the paralysis came on whilst the patient was resting in bed. Of the former three cases one developed sphincter paralysis during a game of cricket, another gave a violent cough whilst in bed with sciatica and was immediately aware of numbness and paralysis of both legs and had sphincter paralysis, whilst the third patient had a profound cauda equina paralysis immediately after manipulation of the back for long-standing sciatica.

Case 2.—J. B., a woman aged 33 (R.I. 16687), had an attack of right-sided sciatica at the age of 16 years. It persisted in greater or less degree for three years, and she was then completely free from symptoms for 14 years until 10 months before admission when, following a mild back strain, there was a gradual recurrence of pain in the back and down the posterior aspect of both lower limbs. Despite various forms of physiotherapy, the pain persisted and after eight months she was bedridden with it. Three weeks before admission, the lumbar spine was manipulated under general anaesthesia. On recovering from the anaesthetic, she was free from pain, but complained of numbness and weakness of the legs, and was unable to empty the bladder.

On examination there was gross distal paralysis of both lower limbs, affecting all the muscles supplied by the lowest lumbar and all the sacral nerve roots. The knee jerks were present, the ankle jerks absent, as also were the plantar responses. There was deep sensory loss along the lateral border of the feet, on the posterior aspects of the legs and thighs, over the buttocks and perineum, that is, the areas supplied by the fifth lumbar and all the sacral roots. There was retention of urine and incontinence of faeces, with loss of the anal reflex. The cerebrospinal fluid contained 200 mg. protein/100 ml.

There seemed to be clear evidence of compression of the cauda equina and at operation a large protrusion of the lumbo-sacral disc was removed.

Recovery was slow. Improvement in motor power and sphincter control continued for three years, but when last seen nine years after operation, the patient still had a slightly waddling gait and also sensory loss. The vesical sphincter had improved to the point where by taking care she could avoid incontinence, but there was still occasional rectal incontinence.

Symptomatology

Pain.—As noted above practically all these patients had pain of greater or less degree before the onset of paralysis, and in character and distribution it resembled that of the common lumbar disc lesion. It is significant, however, that 14 patients had bilateral sciatic pain in the paralytic attack, although it was usually much more severe on one side than the other. It is also interesting that four patients experienced sudden and dramatic relief of pain with the onset of paralysis. I have known this to occur in many cases of sciatica with the onset of a drop foot and it must mean that severe compression has abolished pain conduction as completely as that of the motor impulses.

Two patients had very little pain, and the diagnosis in such cases may be very difficult. One of these patients awoke one morning with a profound cauda equina paralysis and only on subsequent questioning would he admit to having had, for three weeks before the onset of paralysis, slight discomfort in the back and in the right sciatic distribution. A disc protrusion was found at L.5–S.1. The other case was very unusual in having had little pain and no demonstrable sensory loss.

Case 3.—E. F., a man aged 52 (R.I. 82610/47), was referred because of the discovery of a high protein content in the C.S.F. in the course of investigation for retention of urine.

The story was that 10 years previously he had suddenly developed incontinence during a game of cricket. This cleared up, except for stress incontinence, within a few days. Eight months before admission he developed chronic retention with overflow and a month later an attack of acute retention led to emergency admission to another hospital. A suprapubic cystostomy was done and he returned to work as a gardener. At a subsequent admission to see if any cause could be found for the sphincter paralysis, a lumbar puncture revealed a great excess of protein in the cerebrospinal fluid and he was accordingly referred for a neurosurgical opinion.

This patient denied having had sciatic pain at any time, but he had had mild lumbago five years previously which had neither incapacitated him nor led to his seeking medical advice. His bowels moved normally with no incontinence, and sexual functions were normal.

On examination, the patient was a healthy looking man. He had learned to manage the suprapubic cystostomy so that it was only a minor inconvenience. Movements of the lumbar spine were normal, and there was no demonstrable weakness of the lower limbs. The reflexes were normal except that the left ankle jerk and the left cremasteric reflex were absent. There was no demonstrable sensory defect. Radiographs of the vertebral column were normal. Lumbar puncture in the fourth lumbar space revealed a manometric block, and the cerebrospinal fluid contained 520 mg. protein/100 ml. Myelography demonstrated an obstruction opposite the second lumbar disc. At operation a small calcified protrusion of the second lumbar disc was found. It was obviously too small to cause compression of the theca and its contents, but on opening the theca a dense band of fibrous thickening of the arachnoid was found. It was so thick and opaque that the roots of the cauda equina could not be seen through it, although above and below this lesion the leptomeninx looked normal.

Five years after operation he reported no significant change, but said that he had had some back pain and right-sided sciatica at times, but it was in no way disabling.

Paralysis of Muscles.—In 11 cases there was profound paralysis. This usually involved the anterior tibial and peroneal groups and the calf muscles, although in some cases one group was affected more than another and the legs were involved asymmetrically. The functional effect was profound paralysis of the legs and feet, and if an incomplete lesion it was usually a unilateral or bilateral foot-drop. In six cases there was no significant motor paralysis, in which cases the disturbance was limited to sensory and sphincteric functions.

The ankle jerks were absent on both sides in 16 cases, on one side in six; in a single case both were present although they were previously known to have been absent.

Sensation.—In all but one case (Case 3 above) there was objective sensory loss, characteristically in the whole sacral distribution and involving all modalities. When the sensory defect was so complete and extensive, the patients were often aware of numbness, but in some cases they did not seem to have noticed it until their attention was called to it. In 11 cases the sensory loss was less complete and was often asymmetrical, that is, there was complete loss in the whole sacral distribution on one side but in the other side the loss was limited to the perianal and perineal region. In five cases the loss was confined to a small area around the anus and in the perineum. Such cases emphasize the importance of a complete sensory examination, as it may provide the only objective evidence of a neurogenic cause for sphincter paralysis.

Sphincters.—Some degree of paralysis of the anal and vesical sphincters occurred in all but two of the 25 cases. In 14 it was complete with retention of

urine and a patulous anal sphincter leading usually to faecal incontinence. In the rest there was something short of this, for example, intermittent retention, loss of vesical and urethral sensation, or constipation with defective anal sensation. Complete (double) sphincter paralysis was always accompanied by profound bilateral sensory loss in the saddle area, often in the whole sacral distribution. In some of these cases there was a remarkable escape of motor power, that is, the patient had complete sphincter paralysis, extensive sensory loss, absent ankle jerks, and yet no muscular paralysis. We have encountered only one case of significant sphincter paralysis due to a disc lesion in which the sensory and motor defects were strictly unilateral, whilst in Case 3 (above) the paralysed bladder was accompanied by neither motor nor sensory deficit. That sphincter paralysis is so common a feature in this series is understandable because it is usually this complication which leads to their admission to hospital: although the preceding pain may have been the most severe yet experienced, the patient and his doctor are familiar with it, and defects in sensation and motor power may not be very obtrusive when the patient is already in bed. But everyone appreciates the gravity and inconvenience of sphincter paralysis and there is usually no delay in seeking admission to hospital once it occurs. And it is often this symptom alone which demands operation, that is, the pain has often cleared up and the sensory and motor deficits are not enough in themselves to warrant operation.

Investigations

Plain Radiographs.—As in other cases of intervertebral disc lesions, radiographs were of value chiefly in excluding other causes of cauda equina compression, such as intraspinal tumour. In seven cases there was some narrowing of the appropriate disc space, and in six others there were local arthritic changes, but in none were the radiological features regarded as diagnostic.

Lumbar Puncture.—As the majority of these lesions occur in the fourth and fifth lumbar discs, lumbar puncture at the usual site (third or fourth interspace) will often be above the lesion. Even so, in each of the 21 patients from whom fluid was obtained there was an increase in the protein content. This varied from 55 to 590 mg./100 ml., with more than 100 mg. in 15 cases. In three patients specimens were obtained from both above and below the lesion, and a manometric block was demonstrated between the two sites of puncture. In two of these the fluid was xanthochromic both above and below the lesion, the protein content being 500 mg. in both specimens in one case and 590 mg. below and 100 mg. above in the other. In the third case the values were 70 mg. above and 90 mg. below. It was not possible to correlate the variations in the protein content of the fluid with either of the two types of lesion encountered at operation. It might have been supposed, for instance, that the cases in which there was fibrous thickening of the arachnoid would have shown higher protein contents in the fluid whether from above or below the lesion, but that was not constantly so: indeed both the highest and the lowest protein contents were found in cases with marked arachnoid thickening.

In all cases in which the puncture was done below the lesion, a partial or complete manometric block was found. In two cases repeated efforts failed to obtain any fluid, a common experience with other expanding lesions of the cauda equina.

Myelography.—This was done in 18 cases, in 16 of which there was a complete obstruction to the passage of the opaque medium. In most there was an irregular margin at the site of the obstruction, suggesting an extrathecal lesion, but in two cases there was a smooth, rounded margin as is commonly seen with intrathecal neoplasms. The opaque substance was in each case introduced into the lumbar theca, either above or below the lesion, and thus either the upper or lower margin of the lesion was demonstrated.

Findings at Operation

With the exception of Case 1, all patients were operated on. The site of the lesions is indicated in Table I.

TABLE I

SITE OF LESION

Lumbar Disc	Cases in Series	Reported Cases
1	—	1
2	1 (+ case 1)	5
3	3	11
4	10	11
5	12	6
	26*	34

* In two cases lesions were found at both fourth and fifth spaces.

It will be noted that 22 of the 26 lesions occurred at the common sites associated with uncomplicated sciatica. In the two cases with double lesions it was the two lower spaces that were affected.

In 17 cases there was a massive loose fragment largely filling the vertebral canal, behaving much as an extrathecal tumour. In the remainder the protrusion although large was no larger than is often seen in cases of ordinary sciatica, but in each

of these the theca was opened and focal thickening of the arachnoid was found. In these cases the changes in the arachnoid seemed to be of more importance than the size of the disc lesion. It is interesting that the patients with arachnoid changes had on the whole no longer histories than those without such changes, and that in three of them, without any massive disc protrusion, the onset of the cauda equina syndrome was sudden.

These arachnoid changes may also account for persistence of a myelographic obstruction after the protruded disc material has been removed. This is not surprising, as it is unlikely that removal of an extrathecal mass would have any immediate effect on structural changes within the theca. That a clinical problem exists, however, is demonstrated by the following case.

Case 4.—B.C., a woman aged 27 (R.I. 186976/54), had suffered from six attacks of back pain each of a week's duration since a trivial back strain six years previously. Three weeks before admission bilateral sciatica supervened in one of her attacks. A fortnight later she awoke to find weakness and numbness of the legs and she had retention of urine.

On examination there was a profound flaccid weakness of both legs, but the paralysis was not quite complete, that is, there were feeble movements of the toes and ankles. The ankle jerks were absent and there was sensory loss below L.5. Puncture at the L.4–5 interspace revealed no manometric block and the C.S.F. protein was 65 mg./100 ml. Myelography (from below) showed a complete block at L.3–4, however.

At operation a moderate-sized lesion was removed from the L.3–4 level extrathecally. There was no immediate improvement but in fact some deterioration in motor power. She was screened again the day after operation and the opaque medium was found to be immobile. Subsequently a cisternal injection was made but this too was completely held up at the site of the original lesion. It was decided to re-explore lest a fragment of disc had been missed and this was done 14 days after the first operation. No disc material was seen so the theca was opened and the arachnoid was found adherent to it. There was no subarachnoid space, only a little loculated C.S.F., and the roots were adherent to the arachnoid. No attempt was made to separate the roots. Progress from that time was very slow.

Although persistence of a myelographic abnormality after operation may thus be due to arachnoid adhesions, the possibility of there being two lesions must be remembered. In one case in the present series, a persistent defect led to re-exploration with the discovery of a second lesion at the space below that originally explored.

Post-operative Course and Long-term Follow-up

In addition to Case 1, who died unoperated, one patient died nine days after operation from unassociated pathology, though operation doubtless initiated her final collapse (Case 5). All the remaining patients have been followed up since their discharge from hospital, some for as long as 14 years. Only four of them have made complete recoveries as regards muscular power, sensation, and sphincter control.

It is widely known that recovery from cauda equina lesions is slow but it is doubtful if it is realized just how unsatisfactory it can be. In general the motor recovery is better than the sensory and all the surviving patients are walking again. Once the compressing lesion has been removed motor recovery occurs slowly by regeneration, as in a peripheral nerve damaged in continuity. As O'Connell (1950) has pointed out, the sensory lesion in these cases is proximal to the posterior root ganglion and if it is severe enough to cause degeneration there can be no improvement. That some sensory recovery occurs is due to the fact that at the outset the lesion is not complete and some partially damaged roots ultimately recover. Sphincter paralysis is often the most serious aspect of the problem for obvious reasons, and a patient may become fully ambulant, free of pain, and in no way inconvenienced by sensory loss, yet still not have adequate control of the sphincters. It may be three or four years before the end state in regard to sphincter control is reached, and the patient will need a good deal of encouragement and reassurance during this time, in addition to careful observation of the urine to ensure that chronic infection does not do irreparable damage.

Of the few who still had back pain or sciatic pain at the time of operation, all were relieved immediately, and there has been no recurrence of pain except in Case 3 in which there was profound arachnoid thickening. In general, the patients with arachnoid changes recovered more slowly and less completely than those in whom there was a massive compressing lesion without arachnoid changes.

Paralysis of the limb muscles may persist for two to three months after operation before there is any sign of recovery, and improvement once started continues only very slowly. It is difficult to assess the rate of progress but it appears that the greatest improvement occurs in the first two years after operation, although several patients have professed continuing improvement after as along as five years. Some of this protracted improvement is probably due to the patient learning to make better use of permanently weakened muscles, as occurs in other cases of static paralysis. Of the seven patients who have left hospital having had significant paralysis before operation only two have made complete

motor recoveries. All the remainder are fully ambulant, however, most of them with only a slight limp. The ankle jerks were still absent at the most recent examination in 11 cases, while in two others they returned at the second and third year respectively.

Sensation usually recovers more slowly and less completely than motor power, and it was possible to demonstrate some impairment in the pre-operative distribution in 11 cases up to nine years later. The loss is commonly less profound and extensive, however, and usually causes no inconvenience. None of the patients is known to have developed trophic changes.

Of the 14 patients who had total paralysis of the bladder and bowel before operation and have left hospital, only two have regained full control and sensation (Table II). Seven acquired full control of the bladder and are never incontinent but they have defective vesical and urethral sensation and several are occasionally incontinent of faeces. The rest have occasional incontinence but in only two is this so frequent that an appliance has to be worn. All but one have been followed for a year, and nine for over four years.

In general the bowel recovered less well than the bladder and there are only five patients who are not occasionally incontinent of faeces. In two of these the bowel has recovered more completely than the bladder.

Of the 14 males we have precise information about sexual activity in only four. One is impotent and three say they are normal. It is interesting to note that in two of these recovery of the bladder and bowel had been incomplete and there is some continuing defect in sensation in the lower sacral segments.

TABLE II

DEGREE OF RECOVERY IN 14 CASES IN THIS SERIES WITH COMPLETE DOUBLE SPHINCTER PARALYSIS

Case No.	Compression-operation Interval	Bladder	Bowel	Sexual Function	Length of Follow-up (yr.)
1	1 month	F	F	—	13
3	3½ weeks	F	F	—	2 2/12
5	2 weeks	G	F	Impotent	4
7	3 months	F	G	Normal	5
9	1 week	P	G	—	5
11	2 weeks	VG	VG	Normal	5
12	3 days	G	G	—	5
14	3 weeks	VG	F	—	9
15	2 months	G	G	Normal	13
16	2 weeks	G	P	—	4
17	2 weeks	G	NM	—	1
23	2 weeks	G	G	—	1
20	1 week	VG	VG	—	1 4/12
25	7 months	—	—	—	Nil

VG = perfect.
G = perfect control, no incontinence, but imperfect sensation.
F = occasional incontinence, not requiring permanent precautions.
P = requires appliance.
NM = no mention.

TABLE III

POST-OPERATIVE COURSE (CASES IN THIS SERIES AND FROM LITERATURE WITH SUFFICIENT INFORMATION)

Degree of Recovery	Perfect	Perfect Control	Occasional Incontinence	Requiring Appliance
Motor				
Present series ..	8	3	2	2 (=15)
Literature ..	8	8	9	3 (=28)
Total	16	11	11	5 (=43)
% (of total) ..	37	26	26	12
Bladder				
Present series ..	6	6	4	1 (=17)
Literature ..	11	5	—	1 (=17)
Total	17	11	4	2 (=34)
% (of total) ..	50	32	12	6

Discussion

Our experience accords fairly closely with the 34 other recorded cases which we have analysed. In these there was a striking preponderance of males at and past middle life. Two cases followed a major spinal injury without fracture, the diagnosis being made, in the presence of normal manometry, by myelography (Schneider, 1949). One case (Dandy, 1929) followed therapeutic manipulation for bilateral sciatica, a massive prolapse at L.3–4 being found subsequently. Three other cases (Ver Brugghen, 1945) of sudden onset were related to a violent sneeze or cough, whilst a fourth patient (Tolosa and Ectors, 1953) related the onset of the cauda equina syndrome to stooping down to pick something off the floor during an attack of sciatica. Two-thirds of the patients had long histories of recurrent backache and sciatica and over half of them had bilateral sciatica in the compressing attack. Profound paralysis occurred in all but three, whilst the ankle jerks were absent on both sides in 25 cases, on one side in six and were present in two cases. Sensory loss in the saddle area was found in 24 of the 28 cases in which a sensory examination was recorded. Complete sphincter paralysis is mentioned in 22 cases. A high protein content in the spinal fluid from below the level of the lesion is frequently found but there is no record of high values from above the lesion.

Myelography was done in 22 cases and in all of them a gross lesion was demonstrated but the difficulty of differentiation between a disc lesion and a neoplasm seems to have been considerable. French and Payne (1944) say that on the basis of the myelogram five of their eight cases were operated on with the diagnosis of tumour.

The site of the lesion in these 34 recorded cases is shown in Table I. It will be seen that half were in the upper lumbar region as opposed to the common

fourth and fifth lumbar discs, lesions which are responsible for the vast majority of uncomplicated cases of sciatica. Arachnoiditis was reported in three of one series of five cases operated on transdurally (Tolosa and Ectors, 1953).

It is difficult to assess the post-operative course in many of these cases because of insufficient data. It appears, however, that only four of the 34 made complete recoveries—an even smaller proportion than that in this series. (The results, reduced to standards as nearly as possible comparable to this series are set out in Table III, which shows that only 11 were followed for more than six months.) In regard to sphincter recovery, there are two features worthy of note. One is that in most cases there is no mention of the bowel, which we found to recover less well than the bladder. The other is that the number of " very good " recoveries of the vesical sphincter is probably too high, this designation having been awarded (by us) for such comments in the papers as " can control urine " or " bladder working again ". Our experience in following up these patients for long periods is that they often minimise the shortcomings of the sphincters, so pleased are they to have them working at all. More than once there is a note in our records to say " bladder (or rectum) normal " and a later note by a more searching observer mentions significant defects present ever since the operation.

In the literature on spinal arachnoiditis there is little suggestion of a relationship with prolapsed disc until French (1946) reported 13 cases of localized lumbar arachnoiditis explored by operation in which a disc lesion was found in eight, whilst the remaining cases were early ones in which he thought it possible that a small disc lesion might have been missed. The general symptomatology of these cases was similar to those reported in our series but many were less severely disabled. The C.S.F. proteins were much lower than in our series whilst the recoveries seem to have been much less satisfactory with regard to relief of pain.

Several other points emerge from a consideration of our cases and those recorded in the literature. Compression of the cauda equina by intervertebral disc lesions is quite unpredictable although the possibility is slightly greater in patients of middle age and over. Bilateral symptoms and signs commonly precede serious compression and indicate its imminence. There is evidence too that a sudden movement may precipitate a compression lesion, and although we cannot avoid many such movements which occur in the course of daily life, to employ sudden or violent movement (for example, manipulation of the spine) as a therapeutic procedure seems to be risky. We are aware of the fact that the reported cases make up a very small proportion of the vast number of patients who have had manipulations for back pain and sciatica, but that this complication can occur and that it is quite unpredictable, makes us feel that manipulation should not be undertaken without due thought and knowledge of the risks. Eyre-Brook (1952) refers to a case and warns against manipulation. The question has obvious medico-legal importance.

Diagnosis is usually not difficult. The considerable elevation of the spinal fluid protein content may lead to the suspicion of a neoplasm, but the presence of a myelographic obstruction would indicate an exploration in either case. It should be mentioned that myelography is important in revealing the site of the lesion, as in five of these cases, and in half of those reported in the literature, the lesion was above the fourth and fifth discs, the ones usually explored in cases of sciatica. Myelography is also of value in indicating the presence of two lesions, one of which might not have been suspected from the clinical evidence.

One condition with which compression may be confused is the diabetic myelopathy described by Garland and Taverner (1953). The five patients described in their paper all had sciatic pain, muscle weakness, and absent tendon reflexes ; four had raised protein in the C.S.F. None had any sensory loss, a useful but not reliable differentiating feature (see Case 3 of the present series), but in three cases there was at some time an extensor plantar response which would have ruled out a cauda equina compression. This problem of the possible relation between diabetes and cauda equina paralysis arose in one of our cases.

Case 5.—M.S., a woman aged 72 years (R.I. 198778/54), a moderately severe and poorly controlled diabetic of 12 years standing, had had an attack of left-sided sciatica six years before admission. Three weeks previously she had a recurrence followed after a week by gradual weakness of the left foot, then by numbness of the whole leg and a week before coming here she developed urinary retention.

She was still in severe pain with very limited spinal movement and straight leg raising diminished to 40° on each side. There was an almost total palsy of the left foot with sensory loss in the entire sacral distribution on the left and in the lower sacral segments on the right as well. The protein content of the spinal fluid was 120 mg./100 ml. and there was a complete block at L.4–5 on the myelogram. The blood pressure was 220/110 mm. Hg and the blood sugar 290 mg.

At operation a large loose fragment was found completely extruded from the disc space and several smaller ones still in the space. She was relieved of pain but there was no other striking change in her neurological state in the nine days during which she survived. She

went gradually downhill, finally developing diabetic coma. At necropsy there were bilateral hypernephromata replacing most of the renal tissue, the blood vessels were in good condition, but the bladder was severely inflamed; there was no evidence of ascending urinary infection.

When operating for cauda equina paralysis some modifications of the technique used for uncomplicated cases of sciatica may be necessary. A more liberal exposure must be made, if necessary a full bilateral laminectomy, in order to see the lesion and avoid too vigorous retraction of the theca. If to approach the lesion extrathecally entails too much retraction (and in many of these cases the spinal canal is tightly filled) there must be no hesitation in opening the theca. The roots are then separated and the anterior theca over the bulge incised. As soon as the massive fragment, which is usually found in these very tight cases, is removed there is plenty of room and the exenteration of the disc space may be completed by the ordinary extrathecal approach. There is no need to close the incision in the anterior theca but that in the posterior is closed in the usual manner.

That operation for uncomplicated sciatica may not guarantee against a subsequent compressive lesion developing is shown by the following case.

Case 6.—C. N., a man aged 61 (R.I. 22631/42), first attended in 1942 when he was 57. He had had bilateral sciatica and paraesthesiae in the sacral distribution on and off for 10 years. At operation a moderate protrusion was removed from L.4–5 on the right. He made a complete recovery and remained well until 1946.

He returned then with the complaint that since "ricking his back" eight months previously he had suffered a gradual onset of backache and bilateral sciatica (worse on the right). Symptoms had been progressively worsening in the last four months and he had been in bed for two months, during which time he had noticed progressive weakness of the legs. Incontinence of faeces and hesitancy and difficulty with micturition had come on two weeks before admission.

There was marked bilateral palsy with wasting, including the buttocks, bilateral sensory loss in S.3, 4, and 5, and absent ankle jerks. Lumbar puncture at L.2–3 showed no block and the protein was 120 mg./100 ml.

At operation the dura was opened and matted bluish-red roots were found stretched over a massive protrusion just to the right of the centre at L.4–5 (the site of the previous lesion); there was a massive free fragment. He left hospital six months after operation with little motor improvement but able to void in the sitting position. Within a year he could walk 40 yards without sticks, and a year later, according to a letter from him, was indulging in gardening and fishing.

This is the only instance that we know of in which serious compression has occurred after an operation for an intervertebral disc lesion. It is, however, an argument for a radical operation, if an operation is to be done at all, for all lesions no matter how simple. Removal of only the protrusion causing visible compression of a root is not sufficient and should be followed by vigorous exenteration of the interior. In operating for ordinary uncomplicated sciatica we have found on many occasions large loose fragments of annulus fibrosus in the interior which might well have been extruded subsequently had they not been removed at the time.

In these cases we found no evidence that the degree of recovery was related to the time interval between the onset of compression and the operation (see Table II). Nevertheless there is everything to be said for operation as soon as possible after the onset of paralysis. Indeed an emergency operation in a rapidly progressive case might prevent complete paralysis. That is to say that a patient who has pain, incipient weakness, and sensory loss might be spared sphincter paralysis if operated on in time. It might also be that the chances of arachnoid adhesions developing are lessened the sooner the compression is relieved.

Summary

Twenty-five cases of cauda equina compression due to a verified prolapsed intervertebral disc are described, including two fatal cases. The symptomatology, clinical details, and results of lumbar puncture and myelography are discussed, together with the operative findings and follow-up after leaving hospital.

Thirty-two further cases culled from the literature, including one fatal but unverified case, are reviewed.

The incompleteness of recovery in most cases and the possibility of a fatal issue are stressed. Attention is drawn to the risk of precipitating this serious complication by manipulating uncomplicated cases of sciatica believed to be due to prolapsed intervertebral disc.

I wish to thank Mr. J. B. Pennybacker for his constant help and encouragement in the preparation of this paper. All the cases reported were under his care.

References

Dandy, W. E. (1929). *Arch. Surg.* (*Chicago*), **19**, 66.
——(1942). *J. Amer. med. Ass.*, **119**, 474.
Eyre-Brook, A. L. (1952). *Brit. J. Surg.*, **39**, 289.
French, J. D. (1946). *Surgery*, **20**, 718.
——, and Payne, J. T. (1944). *Ann. Surg.*, **120**, 73.
Garland, H., and Taverner, D. (1953). *Brit. med. J.*, **1**, 1405.
Kaplan, A., and Umansky, A. L. (1951). *Amer. J. Surg.*, **81**, 262.
Kennedy, F., Hyde, B., and Kaufman, S. (1948). *J. nerv. ment. Dis.*, **108**, 32.
Mixter, W. J., and Barr, J. S. (1934). *New Engl. J. Med.*, **211**, 210.
Nicaud, P. (1947). *Sem. Hôp. Paris*, **23**, 2065.
O'Connell, J. E. A. (1944). *Surg. Gynec. Obstet.*, **79**, 374.
——(1950). *Ann. roy. Coll. Surg. Engl.*, **6**, 403.
Rouqués, L., David, M., and Pautrat, J. (1948). *Bull. Soc. méd. Hôp. Paris*, **64**, 18.
Schneider, R. C. (1949). *J. Bone Jt Surg.*, **31A**, 566.
Stookey, B. (1927). *Arch. Neurol. Psychiat.* (*Chicago*), **17**, 151.
Tolosa, E., and Ectors, L. (1953). *Acta neurol. psychiat. belg.*, **53**, 431.
Ver Brugghen, A. (1945). *Surg. Gynec. Obstet.*, **81**, 269.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 117.

E.E.G. ABNORMALITIES FROM THE TEMPORAL LOBE STUDIED WITH SPHENOIDAL ELECTRODES

BY

G. PAMPIGLIONE and J. KERRIDGE

From the Institute of Psychiatry, Maudsley Hospital, London

In the last few years applied electrophysiology has played an increasing part in the routine clinical work of many neurological and psychiatric centres. Combined clinical and electrophysiological observations have shown the problem of the epilepsies to be very intricate, and the study of abnormalities of cerebral function related to the initiation and spread of an epileptic seizure still largely awaits development of new techniques. The seizures which Hughlings Jackson (Taylor, 1931) classified in the uncinate group (and which more recent workers have called either "psychomotor" or "temporal lobe" epilepsy) have lately aroused an increasing interest. (The literature is reviewed in papers by Penfield and Jasper, 1954 ; Hill, 1953 ; Meyers, 1954 ; Gastaut and others, 1953 ; Magnus, 1954). Routine clinical electroencephalography has contributed to the study of these types of seizures but only the posterior half or two-thirds of the lateral aspect of the temporal lobe may be explored with scalp electrodes. Anatomical considerations suggest that the activity of the anterior third of the temporal lobe, and particularly that of its inferior and uncal areas, cannot be satisfactorily recorded with electrodes placed on the skin (scalp or zygoma) or even in the pharynx or in the external auditory meatus.

The region of the foramen ovale appeared to be a suitable area easily reached, from which to record the activity of the anterior inferior regions of the temporal lobe. Jasper (1949) mentioned the use of needle electrodes in the region of the greater wing of the sphenoid (" ala magna " electrodes) introduced by Kristensens and Reyes (1949). Penfield and Jasper (1954) show an *x*-ray picture of these electrodes introduced by the anterior approach. The insertion of needles close to the foramen ovale with an anterior approach is, however, a rather elaborate procedure (Penman, 1953) with some risk of entering the cranial cavity through the foramen.

In 1951 D. P. Jones showed to the E.E.G. Society records taken with sphenoidal needle electrodes using the lateral approach. Pertuiset and Capdevielle-Arfel (1951) and Kerridge (1952) reported on their experience with similar methods, but in all these communications the technical details and observations are scanty.

A simple and safe method with slight modification of those previously mentioned has been followed in examining our series of patients. Needle electrodes are introduced through the skin under the zygomatic arch to the vicinity of the foramen ovale. The method described here has become part of the routine investigation of cases in which on clinical or electroencephalographic (E.E.G.) grounds an " epileptogenic abnormality " of one or both temporal lobes is suspected (Hill, 1953 ; Falconer, Hill, Meyer, Mitchell, and Pond, 1955). This paper presents a summary of our experience of 250 consecutive records obtained from 166 patients using this technique up to June, 1953.

Material

All patients had had previous routine E.E.G. investigations (in some as many as 15 records) over a number of years with a total of 824 records. Most of our patients (the majority being under the care of Dr. D. Hill and Dr. D. A. Pond) were selected on clinical grounds irrespective of the previous E.E.G. findings. Most of them had a history of seizures of one or more types considered to be commonly associated with abnormality of function of the temporal lobe ; for example, visceral, epigastric, olfactory or gustatory aura, " dreamy states ", or sudden feelings of indescribable fear, any of which may occur either as an isolated phenomenon or else precede a momentary arrest of movement, a simple or complex automatism, or a generalized convulsion. Other patients were investigated because their fits were facilitated by sleep or precipitated by emotion, or because speech disturbances occurred before or after an attack. In yet others, complex, organized, short-lived hallucinations had occurred or else there had been outbursts of violent behaviour with partial amnesia.

As in other epileptics the scalp E.E.G. abnorma-

lities had been variable in site and severity over a period of time. In some instances there had been generalized E.E.G. abnormalities, in others the abnormalities were recorded mainly from one or both temporal regions. Cases with an obvious short duration spike focus outside the temporal areas were usually not re-examined with this technique unless the patient had more than one kind of attack. Patients with a history of attacks of doubtful nature either with normal or with abnormal scalp E.E.G.s were included as well as some patients who had episodes of altered behaviour either with or without alleged amnesia.

Rarely, in the present series, the indication for proceeding to a " sphenoidal recording " was based on E.E.G. findings : (1) Some non-focal abnormality over the scalp of the inferior fronto-temporal regions ; (2) the presence of bilaterally synchronous runs of rhythmic 2 to 6 c./s. waves ; (3) focal abnormalities with a tendency to shift about the fronto-temporal regions.

Preparation of the Electrodes and Technique of Insertion

The aim is to insert a needle electrode so that its tip lies in proximity to the foramen ovale, i.e., fairly close to the uncal region and not very far from the tip of the temporal lobe and the region of the anterior part of the hippocampal and fusiform convolutions (Fig. 1). The technique employed is a slight modification of that commonly used for the lateral approach to the third division of the trigeminal nerve but the tip of the needle electrode should come to lie just anterior to, and below, the foramen ovale avoiding the nerve.

FIG. 1.—The insulated needle electrode is inserted just below the zygomatic arch and its tip lies anterior to, and below, the foramen ovale in the infratemporal fossa.

FIG. 2.—A patient with sphenoidal and pharyngeal electrodes inserted. Note also the electrode in the concha of the ear where little if any muscle artefact appears. Some of the other electrodes have been removed.

An ordinary hypodermic steel needle 5 cm. long and 0·6 mm. in diameter (gauge 23) was insulated, except for 1 mm. at the tip, with a bakelite varnish which will withstand boiling. The insulating coat was prepared with " darmarda lacquer Grade L 3128 " and a thinner obtainable from Bakelite Ltd. (London). The varnish is diluted one part in three of thinner. A first coat is put on the needle, which is then baked at 100° C. for five minutes. After a second coat the needle is again baked at 100° C. for five minutes. A third coat is applied and the needle is baked for 25 minutes at 150° C. The insulation is scraped off for about 1 mm. at the tip of the needle. A light flexible lead is soldered to the hilt of the needle. This ensures good permanent contact, avoids displacement of the needle with heavy crocodile clips, and permits of a quick extraction of the needle by pulling the lead in case of emergency. The needles can be safely washed and boiled, with stilette *in situ*, wrapped in gauze for sterilization. It is advisable to have at least three or four needles prepared since flaws in the insulation coat may be noticed at the last moment.

The patient should lie down comfortably on a couch and should have an empty bladder, as recording may last over one hour. Edentulous patients are asked to retain their dentures, at least during the insertion of the needles, in order to avoid narrowing of the space between the zygomatic arch and the mandibular notch.

The skin on both sides of the face is cleaned with alcohol and marked with a sterile coloured solution, e.g., methylene blue or gentian violet. An oral probe with a mark at 2·5 cm. from one end is used as a ruler. Another oral probe with a small piece of cotton wool dipped in the coloured solution is used for marking the skin. The point of insertion is marked at 2·5 cm. anterior to the incisura intertragica and about 2 mm. below the inferior margin of the zygomatic arch. When this margin cannot be easily palpated, the mark can be made along a line from the incisura intertragica to the point of attachment of the ala nasi (Fig. 2). In patients with very small faces and in children (four were examined between

the ages of 12 to 15 years, none below 12 in this series) the distance from the incisura intertragica may be less than 2·5 cm. (even near to 2 cm.). Care should be taken that the skin is not displaced by the electrode cap, or by the patient smiling or grimacing, or by the operator's finger. It is important in this connexion to palpate again the inferior margin of the zygomatic arch at the level of the mark as the needle has to pass just below the arch. If desired, the skin and subcutaneous tissue may be anaesthetized with 2% procaine. Deep infiltration with anaesthetic should be avoided. When the patient is sufficiently cooperative it seems advisable to insert the needle without local anaesthetic, with the advantage of quicker procedure, no marked difference in pain between the introduction of the anaesthesia needle and the thin needle electrode, and no displacement of the marking either by the fluid injected or by a small subcutaneous collection of blood.

The needle electrode (without stilette) is then inserted at the marked point at right angles to a sagittal plane. The aponeurosis of the masseter muscle is felt with the tip of the needle as a moderately hard tissue which suddenly gives way. The patient often perceives " a peculiar clicking noise " when the fascia is penetrated. The electrode is gently introduced further in the same direction until it hits the bone (about 4½ cm. deep). When bone is felt superficially, then either the zygomatic arch (insertion too far up) or the mandibular bone (too far down) is met ; this is often due to displacement of the skin, and thus of the mark, during insertion. These errors should be corrected by reinserting the needle. The floor of the skull may be met if the needle is directed upwards. Tilting the needle may stretch the masseter and fascia. If no bone is felt by the time the needle has reached a depth of 4½ to 5 cm. in an average face, it can be left in position and it will not be far away from the bone (either the medial wall of the infratemporal fossa or the upper portion of the lateral pterygoid lamina). There is no need for the electrode to remain in contact with the bone and the record is more satisfactory if the needle is not quite in contact with it. The tip of the needle would then lie in proximity, and slightly anterior, to the foramen ovale (Fig. 1).

Should the needle touch or penetrate the mandibular nerve, the patient may suddenly complain of a sharp pain along the lower jaw and the needle should be retracted a few millimetres.

After the end of the record the needles are rapidly withdrawn but compression of the areas for about one minute is maintained.

Method of Recording and Inducing Sleep

All the records were taken with an 8-channel apparatus (Ediswan) with an amplification of 4 mm. for 20 microvolts, time constant of 0·3 seconds, and high frequency cut of 15% at 75 c./s. Recording was always done in series-connected chains, the usual arrangements being those shown in the illustrations. Additional electrodes were placed when necessary over the fronto-temporal, the sylvian, and the zygomatic regions.

In all cases, even though fully studied with scalp electrodes on previous occasions, a routine scalp E.E.G. was taken before the insertion of the needles. This lasted 15 to 20 minutes but usually overbreathing was omitted both to avoid the risk of a seizure or the appearance of increased muscle activity should a mild tetany be induced.

From the work of Gibbs, Fuster, and Gibbs (1948), Fuster, Gibbs, and Gibbs (1948), and from personal experience, scanty E.E.G. abnormalities in the routine records may be more easily demonstrated during the effect of relatively short-acting barbiturates. Either oral quinalbarbitone (" seconal ") (194 records) or intravenous thiopentone (" pentothal ") (28) was therefore usually administered.

Sleep was always obtained with thiopentone but only 80 times out of 194 when quinalbarbitone was used. Fifty-seven patients with quinalbarbitone became drowsy without falling asleep, 28 became restless, and the remaining 29 were apparently unaffected. One of the patients who became restless abreacted and the record had to be interrupted. Quinalbarbitone was given by mouth, the capsules being repeatedly perforated with a pin to facilitate absorption. An initial dose of 3 grains was followed after 25 minutes by additional 1½ grains either if no fast activity (18 to 28 c./s.) appeared in the traces or if the patient was not yet drowsy. The first dose was usually given just before the introduction of the sphenoidal needle electrodes, and recording in the appropriate arrangement began within five to eight minutes before any effect of the drug appeared either clinically or electrically so that the induced changes could be followed.

Usually a period of five minutes of ordinary recording with sphenoidal electrodes in place was allowed before beginning the injection of intravenous thiopentone solution. Thiopentone (" pentothal ") 5% solution was injected intravenously at the rate of 1 ml. a minute irrespective of body weight until the patient was deeply asleep (disappearance of corneal reflex).* The injection was then interrupted but on occasions resumed at the same rate when the patient woke up. The total amount varied from 5 to 19 ml. (0·25 to 0·95 g.) but the second dose was usually much smaller than the first. With thiopentone two patients abreacted violently and two others less dramatically. The abreaction, however, came after a period of sleep and the record was then interrupted. Two of the patients with thiopentone began to cough so much that the record had to be stopped. The first one convinced us of the possible risks (with little advantage) of using pharyngeal electrodes, particularly during intravenous injection of thiopentone.

In our first 200 records, single or bilateral pharyngeal electrodes were introduced as well as bilateral sphenoidal electrodes. Several patients complained that the pharyngeal were more uncomfortable than the sphenoidal electrodes. As no additional information appeared to be given by the pharyngeal electrodes, a single electrode either on the chin or on the tip of the nose was then used

* A trolley with the equipment necessary for resuscitation and artificial respiration was kept at hand though never used.

instead as a less active electrode in a chain including the right and left sphenoidal electrodes.

The effect of auditory, occasionally tactile, or visual stimuli was assessed at various depths of sleep. The patient was eventually awakened and the record continued for a few more minutes. Recording stopped when sleep was not obtained within one and a half hours after administration of quinalbarbitone. Usually before the end of the test a short exploration of the activity of scalp electrodes in other regions than the temporal ones was performed, paying attention to the amplitude and distribution of the barbiturate-induced fast activity. In all the cases when thiopentone was administered and in those without drugs about half an hour of recording gave sufficient information.

Results

Artefacts.—Artefacts were met on occasions mainly in the form of muscle action potentials, and usually disappeared after a few minutes of recording. Artefacts were rarely so troublesome as to mask the underlying activity. In over half of the cases no muscle activity disturbed the traces. Movement artefact was considerable together with muscle activity when the patient swallowed, talked, yawned, smiled, or cried. Pulse artefact was rare and was quickly corrected by pushing the needle one or two millimetres deeper. A very peculiar slow-wave artefact was met in one patient when one of the needles was probably in a small vein and a few drops of blood came out of the hollow needle. Again this was corrected by gently pushing the needle.

Normal Activity.—The activity that we consider normal as recorded with our technique from the " sphenoidal " electrodes is a low amplitude (up to 20 to 30 microvolts) mixture of waves (6 to 15 c./s.), without definite features. Often the trace appears nearly flat. The alpha rhythm is poorly represented, even when prominent over the scalp. When recognizable, it never exceeded about 30 microvolts and disappeared on opening the eyes or following a noise. Mental calculations at times increased the amount of muscle activity. In young subjects a greater amount of 4 to 7 c./s. activity than in adults was recognizable similar to that seen in scalp records from the temporal regions.

Barbiturate-induced fast activity of low amplitude (10 to 30 microvolts) could be seen from the sphenoidal electrodes at the time it appeared from the frontal scalp electrodes (both for oral quinalbarbitone and for intravenous thiopentone). In at least one-third of the cases after quinalbarbitone it was not recognizable at either sphenoidal electrode, but in 48 of the cases no fast activity was seen even from the scalp electrodes. Sleep changes were similar to those recorded from the scalp but sleep spindles were usually less frequently seen. K complexes could be recognized, though of low amplitude, and often showed a phase reversal at each sphenoidal electrode.

Abnormal Activity.—The criteria of abnormality were similar to those generally accepted for scalp recording. A summary of the results obtained in 250 " sphenoidal " records obtained from 166 patients is shown in Tables I to V. The grouping is based on the number of records rather than on the number of patients, as 50 subjects had more than one record taken with this technique. In these cases variations in the amount, type, and lateralization of the E.E.G. abnormalities were often noticed. Seven of our patients had four and one had six records taken with this technique over a period of time ranging from two months to two years.

TABLE I
NO. OF SPHENOIDAL RECORDS IN THE SERIES

No. of Sphenoidal Records in each Patient	No. of Patients	No. of Records
Once	116	116
Twice	26	52
Three times	16	48
Four times	7	28
Six times	1	6
Total	166	250

TABLE II
VARIABILITY OF NORMAL AND ABNORMAL ACTIVITY AT SPHENOIDAL LEVEL IN 50 PATIENTS WITH REPEATED SPHENOIDAL RECORDS

No. of Sphenoidal Records in Each Patient	Constant	Variable	No. of Records
Two	18	8	52
Three	6	10	48
Four	2	5	28
Six	0	1	6
Total	26	24	134

Quantitative differences of the abnormality have been disregarded as only constancy or variability in laterality is considered (at the sphenoidal level).

TABLE III
SPHENOIDAL AND SCALP RECORDS COMPARED

Sphenoidal Records	Scalp Records			Total
	Normal	Doubtfully Abnormal	Abnormal	
Normal	13	27	61	101
Doubtfully abnormal	0	5	7	12
Abnormal	6	21	110	137
Total	19	53	178	250

In the 69 records with bilateral abnormalities at the sphenoidal electrodes one side was frequently more active than the other. The abnormalities were mainly represented by sharp waves or spikes, occasionally by slow waves. Local unilateral

TABLE IV

101 NORMAL SPHENOIDAL RECORDS

Scalp E.E.G.	In-patients with History of Probable Seizures	In-patients with no Definite History of Seizures	Total
Normal	3	10	13
Doubtfully abnormal ..	14	13	27
Abnormal	50	11	61
Total	67	34	101

TABLE V

149 RECORDS WITH DOUBTFUL OR DEFINITE ABNORMALITIES AT SPHENOIDAL LEVEL

Scalp E.E.G.	In-patients with History of Probable Seizures	In-patients with no Definite History of Seizures	Total
Normal	6	0	6
Doubtfully abnormal ..	21	5	26
Abnormal	102	15	117
Total	129	20	149

The site of the doubtful or definite abnormality was at the right sphenoidal electrode in 28 records, at the left one in 52 records, and at both in 69 records.

absence of barbiturate-induced fast activity in connexion with generalized discharges was considered an additional lateralizing sign of the abnormality (Pampiglione, 1952).

The E.E.G. abnormalities recorded from scalp electrodes and those from sphenoidal electrodes were rarely synchronous. Very often two or more focal discharges could be seen from the sphenoidal and temporal scalp electrodes, even though usually only one appeared to contain the elements of shortest duration. In four cases, synchronized discharges appeared which were fairly constantly focal at the same time both at the sphenoidal and homolateral mid-temporal electrodes.

Bilaterally synchronous discharges at both sphenoidal electrodes were very rare indeed and only in two of the 69 records with bilateral discharges at the sphenoidal level was there a predominant bilateral synchrony. In all the others the discharges usually appeared independently on either side. The location and lateralization of the most active focus appeared to change in some patients and not in others when the record was repeated at intervals from a few days to a few months (Table II). In many patients showing focal spike discharges from one temporal area no appreciable changes were recorded from the contralateral homologous region irrespective of the amplitude of the discharge. Very often large sharp waves or spikes recorded from sphenoidal electrodes were not represented by appreciable changes at the homolateral scalp electrodes (Fig. 3), and in six patients the scalp E.E.G. appeared normal throughout (Table III). The converse was often seen.

In two patients with a history of episodic behaviour disorders, and doubtful seizures, generalized bursts of 3 to 4 c./s. bilaterally synchronous spike-and-wave complexes were recorded from scalp electrodes. These complexes were rarely seen, and then only of low amplitude, from the sphenoidal electrodes, often slightly asymmetrical though bilaterally synchronous. Small amplitude sharp waves or small spikes were seen in addition to, and independently from, the spike-and-wave bursts. In both patients these small independent discharges were seen at the left sphenoidal electrode only.

In six cases of subsequently verified tumours involving the anterior half of the temporal lobe there was predominance of irregular slow waves

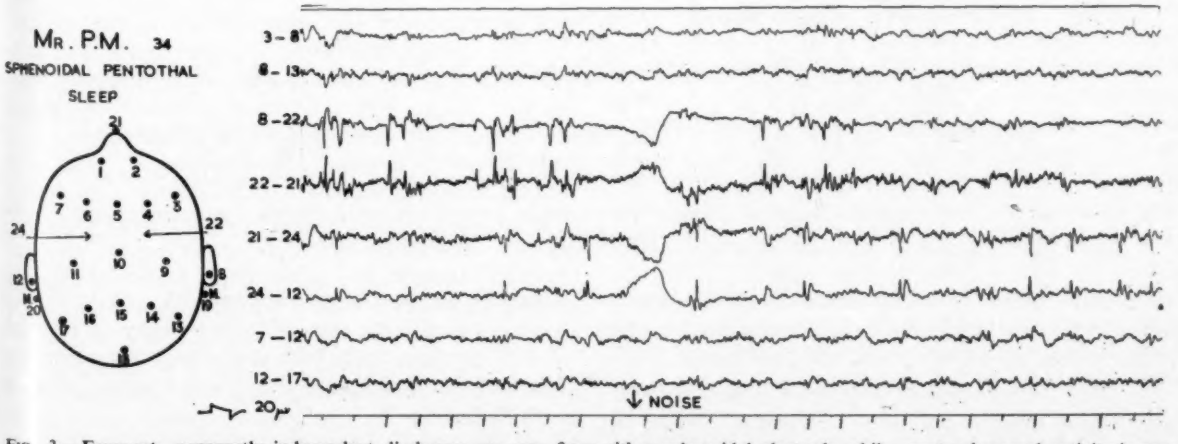


FIG. 3.—Frequent, apparently independent discharges are seen from either sphenoidal electrode while scanty abnormal activity is seen from scalp electrodes. A stimulus (noise) does not, in this case, much modify the abnormality.

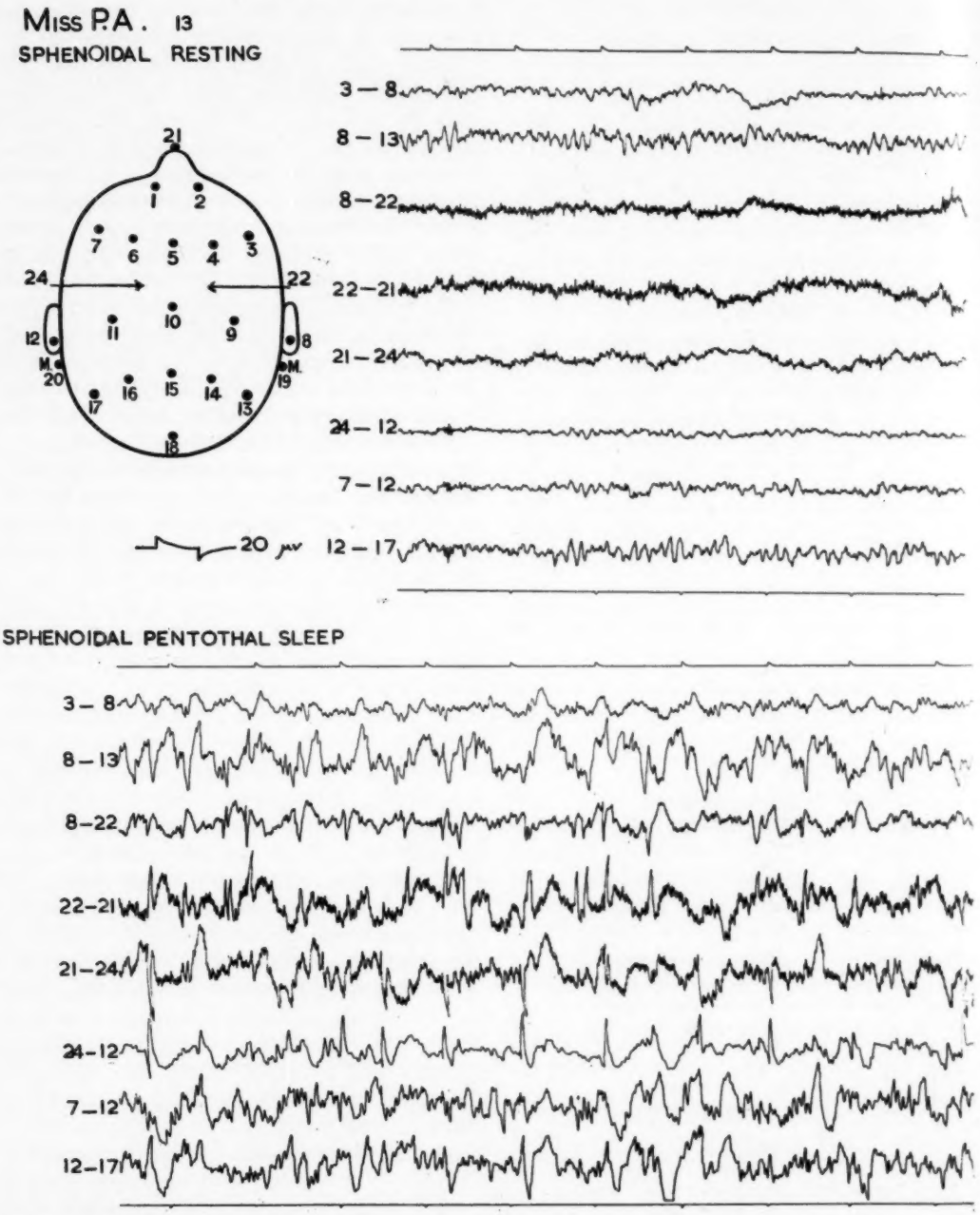


FIG. 4.—Above: the resting record with sphenoidal electrodes showed no gross abnormality. Below: the patient is asleep during intravenous thiopentone injection. A great deal of abnormality is seen from sphenoidal and scalp electrodes. Spikes and sharp waves appear independently over either hemisphere.

with rare spikes or sharp elements at the homolateral sphenoidal electrode, while the barbiturate-induced fast activity was markedly reduced locally.

In five patients a record with sphenoidal electrodes was taken after a unilateral temporal lobectomy. (The operations had been carried out by Mr. M. A. Falconer and included excision of the uncus and anterior part of the hippocampal convolution.) Very little, if any, recognizable activity of cerebral origin appeared to be picked up from the sphenoidal electrode on that side in the first few weeks after the operation.

Barbiturates and Sleep.—The E.E.G. changes induced by barbiturates were also variable. Though

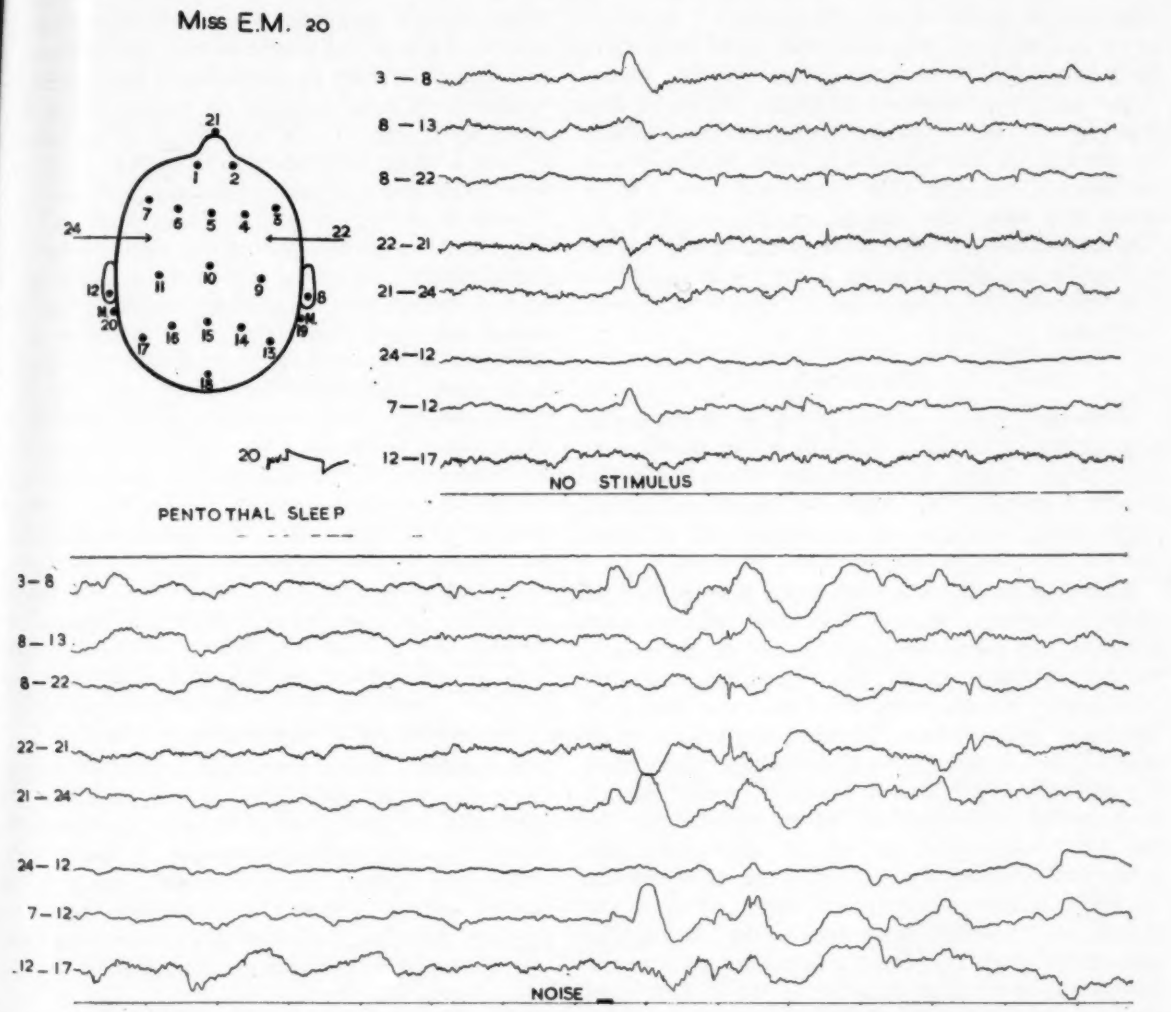


FIG. 5.—Patient asleep under thiopentone. Small unilateral discharges are seen with a fairly constant delay after apparently spontaneous (above) and evoked (below) K complexes.

the abnormalities (particularly spikes and sharp waves) were often increased (35) during the drowsy state or sleep (Fig. 4) sometimes there was no increase in the discharges and in three patients these disappeared during sleep.

In many cases the morphology and often the amplitude of the discharges changed during induced sleep even if the firing rate was not grossly changed. In four patients with unilateral discharges a contralateral independent discharge appeared during sleep (often even more actively firing than the original one) and disappeared again when the patient woke up. No bilateral synchrony was seen at any time in these cases.

During sleep and during the dozing state induced with either drug, sensory stimuli evoked various changes in the records. Apart from the appearance of normal changes (K complexes), a short or prolonged focal discharge followed the stimulus in some cases. In three patients with intense firing, however, the discharges ceased following the stimulus. In two cases unilateral focal discharges appeared only following sensory stimulation during sleep (Fig. 5). Some patients showed E.E.G. abnormalities only at a certain level of sleep and not when too deeply or too lightly narcotized. But some patients showed abnormal discharges only when very deeply asleep, others only when just drowsy. These findings seem to parallel the interesting observations of Lairy-Bounes, Parma, and Zanchetti (1952) for strychnine spikes in rabbits. No adequate interpretation can be offered for these phenomena as yet.

Although intravenous thiopentone offers greater

opportunity than oral quinalbarbitone for the study of various levels of sleep (and this can be done more than once in a few minutes) either drug has advantages and disadvantages (Aungle, Mitchell, and Pampiglione, 1954). Both have fairly similar effects on the E.E.G. No fits were induced by either drug in spite of the fact that occasional very intense firing was seen from one or more areas (Fig. 4). The advantages of using drugs which safely induce a state of changed functional activity of the brain are considerable, particularly in contrast with " metrazol ".

Discussion

Technique.—The insertion of the needle electrodes is a surgical procedure, although a very minor one, and hence should be performed by a medically qualified person. As with all needle punctures, there would appear to be a minimal risk of sepsis but no infection has occurred in our series.

Slight pain accompanies the introduction of needle electrodes but is well tolerated by most patients. As mentioned above, local anaesthesia is hardly necessary, as the fine needle electrodes do not appear to cause more pain than the injection of the local anaesthetic. Some patients have complained of the local paraesthesiae that may follow the infiltration with local anaesthetic. A few patients complained of momentary severe pain along the jaw when the needle had almost reached its final position. We have presumed that this pain was due to the puncture of the mandibular nerve or its sheath as it ceased immediately the needle was withdrawn slightly. Deep infiltration with anaesthetic was avoided in contrast to the technique of Pertuiset and Capdevielle-Arfel (1951) and Jones (1951) as the preservation of pain sensation in the neighbourhood of the mandibular nerve may be a useful guide to the operator. In uncooperative patients we preferred to postpone the test rather than give a general anaesthetic.

We have been reluctant to apply this method in very restless and uncooperative patients and in young children. Similarly, we have also avoided investigating patients during a period in which they are having very frequent fits, as we were uncertain about the consequences of a fit with the needles in place. On two separate occasions one patient, a girl of 19, had a fit immediately after the insertion of one electrode and this was rapidly withdrawn by pulling the soldered lead. The insertion of the needle electrodes would seem to be dangerous only if one goes too far, when it would be theoretically possible to go behind and beyond the pterygoid laminae into the pharynx, or through the foramen ovale into the cavernous sinus and internal carotid artery. Though this would seem to require unusual enthusiasm, it must be remembered that should the foramen ovale be entered, its margin would then direct the needle. The length of our needle electrode is 5 cm. and the above-mentioned points would only seem to assume practical importance in an extremely narrow-faced subject or in young children. The insertion is a simple procedure, well tolerated by most patients, some of whom have had four or more investigations by this technique. Some have stated that they find it not so unpleasant as an injection of " cardiazol " or photic stimulation, and some (admittedly few) have said that it is preferable to the introduction of pharyngeal electrodes. There have been in our experience no sequelae and the investigation has been often done as an out-patient procedure and the patients allowed to go home by public transport, preferably accompanied by a relative, after a few hours' rest.

In only one case the insertion of the needles appeared very difficult on either side. In this patient the radiograph showed an exceptionally shallow mandibular notch ; very little space was therefore available for the horizontal introduction of the needles under the zygomatic arch.

Reliability.—*X*-ray control pictures of the inserted electrodes were taken in 12 of our patients. The variability in the position of the tip of the needle was within 1 c.cm. from the margin of the foramen ovale in 11 people with average faces. In the twelfth patient, with an exceptionally broad and flat face, the tips of the needles fully inserted were 1 in. lateral to the aimed point, though their direction was correct.

In order to check how much variability in placement of sphenoidal electrodes could be allowed for reliable recording, two patients were selected. In both a well localized spike focus at the anterior temporal region was firing frequently. The needle electrode was withdrawn from the original placement in steps of ½ cm. while the record continued. No appreciable change in the shape, duration, or amplitude of the focal spike was noticed up to a withdrawal of about 1½ cm. We consider, therefore, that a slightly imperfect insertion does not appreciably alter the possibility of reliable recording, although a total error of more than 2 cm. (laterally to the foramen ovale) may alter the interpretation of the E.E.G. findings.

Electrodes on the scalp of the fronto-temporal region or in the zygomatic region do not give reliable information on the activity of the inferior anterior temporal region. Electrodes were placed around the fronto-temporal and zygomatic region and their

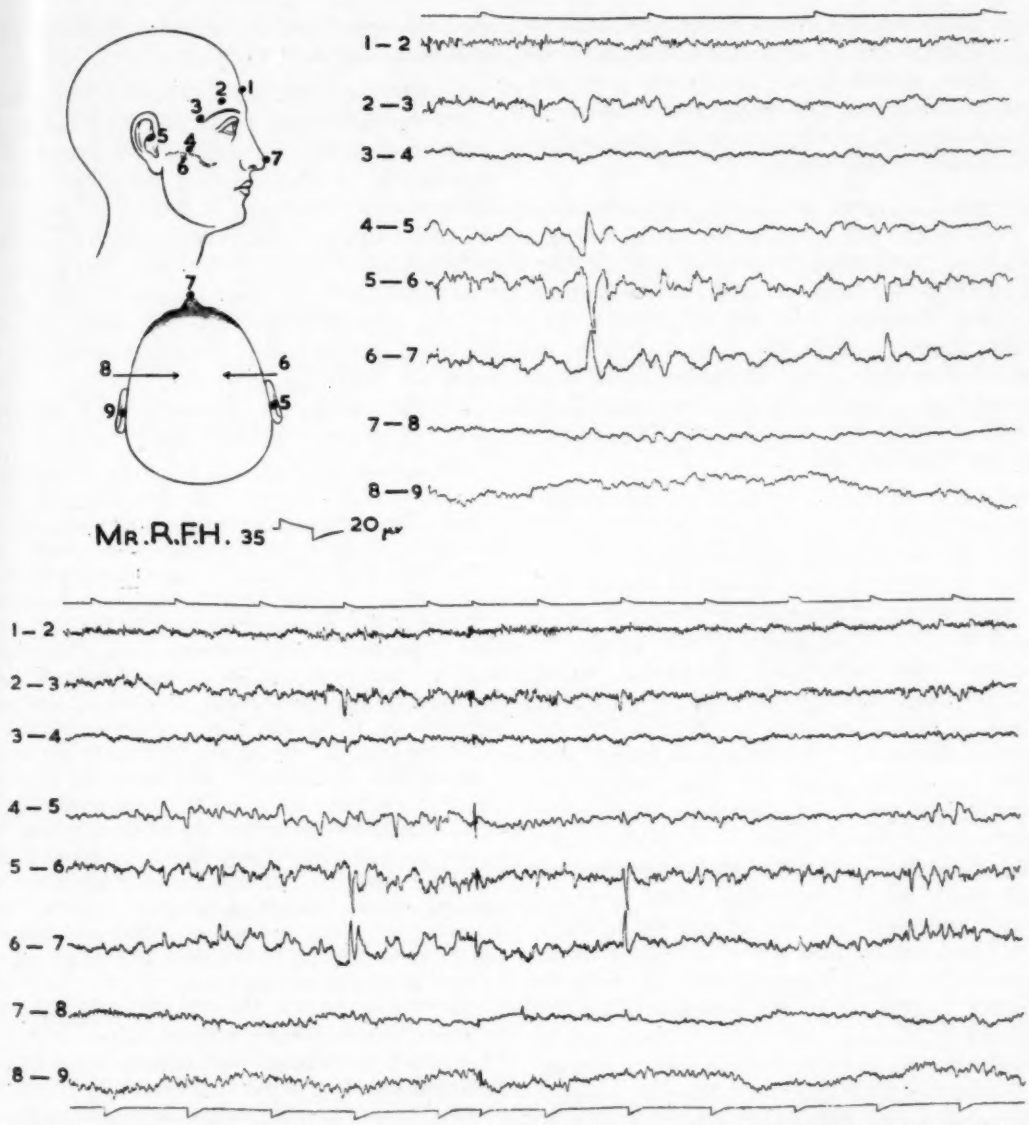


FIG. 6.—The discharges recorded from the right sphenoidal electrode are not always recorded from electrodes placed in the fronto-temporal and zygomatic region. There is no contralateral abnormality (patient awake).

activity was compared with that recorded at the same time from the homolateral sphenoidal electrode (Fig. 6). Though some of the discharges were similar, others were different, suggesting that the activity recorded from the scalp was probably not coming from the same source as that recorded from the sphenoidal electrode.

The reliability of recording with this technique has been checked with direct recording from the exposed brain at operation under local anaesthetic in 13 of our cases. The comparison of direct corticography and sphenoidal records suggests that though the latter method is rather crude in comparison with the former, it gives fairly reliable information. It gives the possibility of differentiating cases in which the discharges are predominantly in the region of the uncus, the anterior part of the hippocampal and fusiform gyrus, or the temporal pole, from cases in which the discharges are predominantly on the lateral surface of the temporal lobe.

"**Mirror Foci**".—In their recent book Penfield and Jasper (1954) define "mirror foci" as "transmitted disturbances from a cortical focus or area in one hemisphere to the homologous area of the opposite side. . . . The primary spike may be shown

to precede that from the mirror focus by 5 to 10 or even 15 milliseconds". They state also that the primary focal discharge is conducted over the principal commissural pathways directly to the opposite side (corpus callosum, anterior commissure, and commissure of the fornix).

In our series of cases the needle electrodes were always inserted on both sides and we could compare the activity of homologous areas in the anterior inferior aspect of the temporal lobe. In 69 cases the abnormalities recorded from the sphenoidal electrode were bilateral (Table V). A close scrutiny of the time-relationships of the discharges from each side showed that simple spikes or sharp waves were very rarely followed by contralateral disturbances within a few milliseconds.

In addition in 80 records most of the abnormalities were unilateral (52 on the left and 28 on the right) and in these cases very rarely could any appreciable disturbance be detected at the contralateral homologous sphenoidal electrode when a spike or a sharp wave appeared on one side. The so-called mirror foci in the abnormal activity of the temporal lobe were therefore in our material very uncommon, at least if we limit the term to Penfield and Jasper's definition. Penfield and Jasper also state that "in some cases the spike and sharp waves from the mirror focus appear just as rapid as those from the primary focus. . . . Even more disturbing is the fact that there may be occasional discharges from the mirror focus which are not immediately preceded by a spike from the primary focus". These conclusions raise the doubt as to whether and when it is justifiable to use the term mirror focus. In addition, if the definition of mirror foci proposed by Penfield and Jasper is used, such a phenomenon was very rare in our material, recording from both the lateral and the anterior inferior aspect of the temporal lobes.

Histological studies of the whole brain of epileptics who showed either unilateral or bilateral E.E.G. discharges in the inferior anterior temporal region might throw some light on this obscure problem. However, it may well be that the distribution of the electrical abnormalities has only an indirect and complex relationship with the distribution of the histologically demonstrable lesions. In the recent paper by Meyers (1954) there is an excellent discussion of the current premises underlying the approach to "the epileptogenic focus" and little at present can be added to it.

The variability in site and morphology of the E.E.G. abnormalities in many of our cases suggests that the demonstrable lesions may be only one of the factors related to the initiation and spread of abnormal electrical discharges.

Underlying Lesions.—Unilateral temporal lobectomy was performed by Mr. M. A. Falconer for the relief of epilepsy in 25 cases of our group and serial histological studies of the tissue removed were performed by Professor A. Meyer (Falconer, 1953; Meyer, Falconer, and Beck, 1954). In the cases where a clear local pathology was found (scars, malformations, or small tumours), this was often in the neighbourhood of the area of maximal electrical abnormality. In other cases the lesions were not discrete.

The following case illustrates some of the problems met in this series of patients :—

J.P., a man, aged 23, was admitted under the care of Dr. Denis Hill. He was right-handed. His birth and infancy were normal. Generalized convulsions began at the age of 2 years and continued infrequently until the age of 12. Then the patient began to have a short-lived feeling of terror, with a peculiar epigastric sensation and the feeling of a threatening person behind him and to his left. This would occur several times a day (up to 10 times). On other occasions these feelings might be followed by loss of awareness, swallowing movements, a far-away or frightened look, trembling of the hands, dribbling saliva, sometimes followed by automatic continuation of activities. On occasions he undressed himself. On other occasions he found himself in a place he did not know. If he had one of these attacks in front of somebody he would not dare to reappear in front of the same person. His attacks were not controlled by anticonvulsants, including a four months' trial of "mysoline". He showed no abnormal neurological signs. A radiograph of the skull and an air encephalogram were within normal limits.

The first E.E.G. in May, 1950, showed focal sharp waves in the right fronto-temporal region. In September, 1951, some intermediate slow activity was seen over the right hemisphere without focal features. A sphenoidal record at that time showed a clear spike focus at the right sphenoidal electrode (Fig. 7). This was more obvious when the patient was drowsy or asleep under quinalbarbitone (gr. 4½). Further scalp E.E.G.s in November and December, 1951, February and October, 1952, and June, 1953, showed generalized abnormalities without constant focal features though maximal in the right fronto-temporal region. Further sphenoidal studies revealed the constancy of the discharge of the shortest duration at the right sphenoidal electrode and no discharges from that of the left sphenoid. A right craniotomy was done by Mr. M. A. Falconer in June, 1953, and corticography revealed frequent abnormal discharges in the temporal lobe, the spikes of shortest duration being most frequently recorded from the anterior temporal region (particularly at the pole). Few abnormal discharges were independently seen in the middle and posterior temporal region and occasionally in the inferior central region. The anterior half of the right

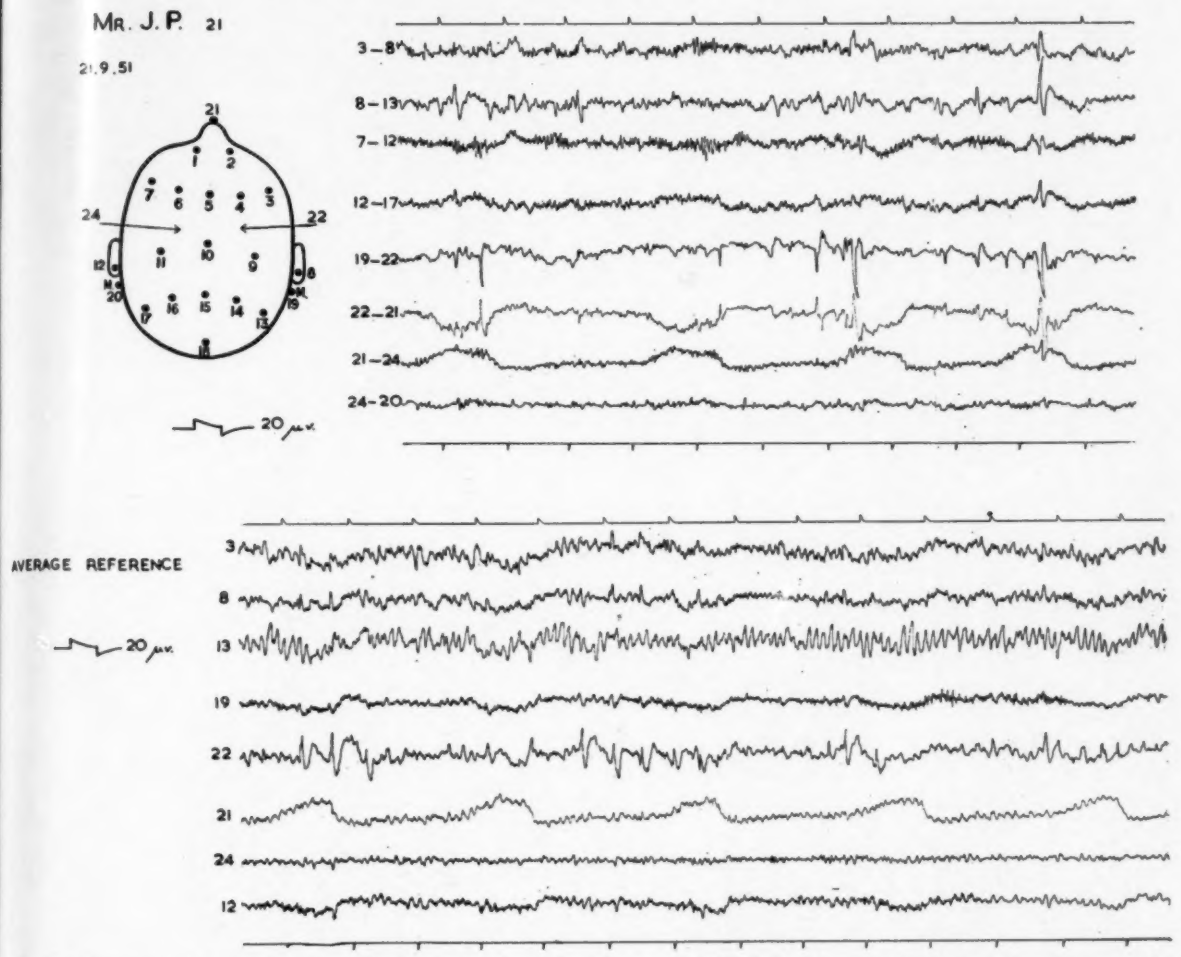


FIG. 7.—Above : standard bipolar chain recording (patient drowsy). Below : average reference recording (patient awake). Electrode 21 is a pharyngeal electrode, 19 and 20 are over each mastoid process, and electrodes 8 and 12 are in the concha of each ear as in most of our records.

temporal lobe, including the uncus and the anterior hippocampus, was removed. No macroscopic abnormalities were recognizable. Histological serial studies of the tissue removed were done by Professor A. Meyer and we are indebted to him for the following report :—

"There was almost total loss of neurons in the Sommer sector (h_1) and the endfolium (h_3-h_5) of the Ammon's horn which thus presented the typical picture of Ammon's horn sclerosis (Fig. 8). This lesion was definitely old and had led to shrinkage although glial fibre stains were not wholly successful. There was also fairly considerable marginal gliosis in all temporal convolutions available, occasionally severe, reaching into the upper layers. The cortex did not show obvious atrophy but showed status spongiosus throughout of a very recent origin, possibly due to oedema (prior to the operation). Status spongiosus was also occasionally encountered in the white matter which otherwise showed no pre-operative changes."

This patient, still on anticonvulsants, in the two years since his operation has had no more attacks of the previous kind, though on a few occasions he has had attacks with clonic movements of the face and jaw apparently in full consciousness.

The removed area, which showed abnormal electrical activity and included histological lesions, was probably involved in the development of some of this patient's seizures. He had never shown contralateral E.E.G. abnormalities, though followed up for a number of years, and had suffered from seizures since early childhood.

In other patients where repeated scalp and sphenoidal E.E.G.s showed multifocal abnormalities it was difficult to decide which area might be the most abnormal one.

The interpretation of E.E.G. findings in relation to the possible distribution of the underlying pathology cannot be discussed at this stage although material is being collected for such a study.

It might perhaps be possible in the future (after a

FIG. 8.—Section of Ammon's horn showing old sclerotic lesion with loss of cells in the Sommer sector and endfolium (patient J. P.). × 10.

much larger series of cases with corticographic and histological studies) to assess whether electrically abnormal areas more active during the effect of barbiturates differ either in underlying pathology or site from areas showing diminished or unchanged activity in apparently similar conditions. Our impression is that the activation or inhibition of the discharges is more likely to be related to the functional state of structures concerned with the appearance or maintenance of sleep than due to a primary local pharmacological effect. The variation in the amount of discharges following sensory stimuli during barbiturate-induced sleep would perhaps be a point in favour of this view (Pampiglione, 1953).

General Considerations

Episodic Syndromes.—Forty-nine patients of our series had a history of attacks of doubtful nature, prolonged hallucinatory episodes, or periods of altered behaviour either with or without alleged amnesia. Clinically most of these patients might have been classified in the large, polymorphous group ranging from hysterical to schizophrenic syndromes. The interpretation of the clinical history sometimes changes in such patients according to the results of the various investigations. In none of these patients, however, did the history include definite epileptic seizures. "Sphenoidal" records were repeated in five of these 49 patients with a total of 54 records. In two repeats out of the five there was a difference between the first and second record, the abnormality recorded at the sphenoidal level being on both occasions unilateral at first and bilateral later.

Of these 49 patients nine (nine records) showed no E.E.G. abnormality either at scalp or sphenoidal electrodes. Fourteen patients (15 records) showed a doubtful abnormality from the scalp but none at the sphenoidal electrodes. In the remaining 26 patients (30 records) the E.E.G. was abnormal at either scalp or sphenoidal level or both. Definite, or doubtful, abnormalities from either one or both sphenoidal electrodes were recorded from 16 patients (20 records).

The lack of any definite history of seizures in these patients appears to introduce additional complications in the clinical evaluation of the E.E.G. findings.

In all the other patients with a definite history of seizures the E.E.G. abnormalities showed a good range of variability. A patient with seizures of the uncinate group may, or may not, show an E.E.G. abnormality only in the anterior inferior temporal region. It is also impossible at present to guess whether in any given clinical case the suspected E.E.G. abnormality will be unilateral or bilateral. In addition, the morphology of the electrical abnormalities recorded in the sphenoidal regions fails to show definite correlation with any particular type of "temporal lobe" seizure, at least in our present experience. In other words, there is no constant correlation between any particular type of clinical attack and the appearance of the E.E.G. abnormalities in the anterior inferior temporal regions. From repeated sphenoidal recordings of a few patients the electrical abnormalities seemed to vary in location and morphology in some, while in others very little change occurred over a period of many months.

We may conclude that this method of recording has given us valuable information about the activity of areas previously rarely explored. However, the gap between clinical and E.E.G. evidence and terminology is still very large.

Summary

A simple and safe method is described for the insertion of needle electrodes to the proximity of the foramen ovale (lateral approach) in order to

study the electrical activity of the anterior inferior regions of the temporal lobes.

The results of electroencephalographic investigations with bilateral " sphenoidal electrodes " are presented in a group of 166 patients largely selected on clinical grounds, an abnormality of function of the temporal lobes being suspected. All patients had previous routine scalp E.E.G.s with a total of 824 records. Two hundred and fifty additional E.E.G.s were taken with bilateral sphenoidal electrodes during the resting state and after the administration of drugs (mainly " seconal " and " pentothal ").

The criteria of normality and abnormality in the electrical activity of the anterior inferior part of the temporal lobes are discussed, including changes occurring during sleep and in response to sensory stimuli. Abnormalities in the E.E.G. taken with bilateral sphenoidal electrodes have been found in some patients in whom repeated routine scalp E.E.G.s were normal. Patients with a history of altered behaviour but without a definite history of seizures may show E.E.G. abnormalities maximal at either one or both sphenoidal electrodes.

The advantages and limitations of this method are discussed. Some observations upon the independence of abnormal activity between the temporal lobes in some epileptics are presented. The study of patients in whom an abnormality of function in the temporal lobe is suspected is considered incomplete without the additional technical procedure described.

Our thanks are due to Dr. Denis Hill, Dr. D. A. Pond, Dr. J. A. V. Bates, and Mr. M. A. Falconer for their advice and criticism, to the technical, recording, and secretarial staff of the Department of Clinical Neurophysiology for their continuous help, to Professor A. Meyer for his kind contribution and photomicrograph, to Dr. R. D. Hoare for his *x*-ray controls, and to Mr. P. V. Jacobs for the photographs.

REFERENCES

Aungle, P., Mitchell, W., and Pampiglione, G. (1954). *Electroenceph. clin. Neurophysiol.*, **6**, 344.
Falconer, M. A. (1953). *Proc. roy. Soc. Med.*, **46**, 971.
——, Hill, D., Meyer, A., Mitchell, W., and Pond, D. A. (1955). *Lancet*, **1**, 827.
Fuster, B., Gibbs, E. L., and Gibbs, F. A. (1948). *Dis. nerv. System* **9**, 199.
Gastaut, H. *et al.* (1953). *Epilepsia* (*Boston*), 3 ser., **2**, 59.
Gibbs, E. L., Fuster, B., and Gibbs, F. A. (1948). *Arch. Neurol. Psychiat.* (*Chicago*), **60**, 95.
Hill, D. (1953). *Proc. roy. Soc. Med.*, **46**, 965.
Jasper, H. H. (1949). II International EEG Congress, Paris, 1949. Rapports *Electroenceph. clin. Neurophysiol.*, Suppl. 2, 99.
Jones, D. P. (1951). *Electroenceph. clin. Neurophysiol.*, **3**, 100.
Kerridge, J. C. (1952). *Ibid.*, **4**, 254.
Kristensens and Reyes (1949). Quoted by Jasper, H. H., 1949.
Lairy-Bounes, G. C., Parma, M., and Zanchetti, A. (1952). *Electroenceph. clin. Neurophysiol.*, **4**, 495.
Magnus, O. (1954). *Folia psychiat.* (*Amst.*), **57**, 264.
Meyer, A., Falconer, M. A., and Beck, E. (1954). *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 276.
Meyers, R. (1954). *Epilepsia* (*Boston*), 3 ser., **3**, 9.
Pampiglione, G. (1952). *Electroenceph. clin. Neurophysiol.*, **4**, 79.
——(1953). *Epilepsia* (*Boston*), 3 ser., **2**, 91.
Penfield, W., and Jasper, H. (1954). *Epilepsy and the Functional Anatomy of the Human Brain.* Churchill, London.
Penman, J. (1953). *Lancet*, **1**, 760.
Pertuiset, B., and Capdevielle-Arfel, G. (1951). *Rev. neurol., Paris*, **84**, 606.
Taylor, J., ed. (1931). *Selected writings of John Hughlings Jackson.* Hodder and Stoughton, London.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 130.

THE EFFECT OF INSULIN COMA AND E.C.T. ON THE SHORT-TERM PROGNOSIS OF SCHIZOPHRENIA

BY

J. HOENIG, D. M. LEIBERMAN, and I. AUERBACH

From the Bethlem Royal and Maudsley Hospital, London

Insulin coma and convulsion therapy have been used very widely throughout the world for the treatment of schizophrenia since their introduction by Sakel (1935) in 1935 and Meduna (1935) in 1934 respectively. Many thousands of patients have been treated in this way and yet the value of these treatments is not established beyond doubt. The problem is still being discussed in emotional rather than factual terms under such headings as " The Insulin Myth " (Bourne, 1953). The correspondence which followed that paper further demonstrated the widely differing views on the subject. This state of affairs does not surprise anyone who scrutinizes the literature which has accumulated over the years, and which contains results which are as diametrically opposed as the following examples illustrate. Gottlieb and Huston (1951) reported on 336 patients of whom 128 had psychotherapy, 65 insulin coma therapy, and 143 electro-convulsive treatment. There was little difference in the outcome of these three groups. On the other hand, Garmany (1946) claimed 56% remissions in cases treated with insulin coma compared with but 2% remissions in those not receiving such treatment. Cossa, Bougeant, and Lombard (1948) found curiously that in comparing insulin-coma treated cases in 1938 and 1944 there was a fall in remission rate from 43·7% to 28%. Kalinowsky and Hoch (1952) and Kalinowsky and Worthing (1943), recognized authorities on physical treatments in psychiatry, regarded insulin coma as inferior to electro-convulsive therapy in this disease. These authors are quoted as examples of the extreme differing and opposing views but theirs are not necessarily the most convincing papers on this topic.

Several workers, such as David (1954), Hughes (1953), Lewis (1945), and Malamud and Render (1939), have discussed the reasons for the confusing results reported, and have criticized the methods of investigation to assess the value of those treatments which have been used in the past. The problem was well summarized by Malamud and Render (1939). They enumerated some of the common errors in the reported studies on the outcome of schizophrenia ; for example, too few cases, inadequate follow-up period, lack of uniformity in evaluating the symptomatology, varying criteria of diagnosis, inadequate examination of material, the variation in the intensity and kind of treatment, and the effect of the preconceived notions of the investigators on the material collected. Lewis (1945) has discussed the inherent difficulties in assessing the psychiatric case material in relation to the same problem.

With such formidable difficulties to be overcome, nothing less than a designed experiment with a suitable control group consisting of several hundred cases and followed over several years would be adequate. Such an undertaking would call for large resources and several years of observation, and so far no such study has been reported in the literature. Nevertheless there have been a number of valuable studies which, although not ideal, obviate some of the above-named errors. For instance, Silverman (1941), at the Meninger Clinic, and West, Bond, Shurley, and Meyers (1955) with his co-workers at the Philadelphia State Hospital have used material where the treated and control group both came from the same clinic. They have assessed results by comparing groups of patients who were admitted before and after the advent of the physical methods of treatment. Such an approach will tend to minimize errors such as differing standards of diagnosis or extreme variation in the admitted case material. It also minimizes differences in the general management of patients, and marked variations in the application of therapy. Another problem is that of excluding the bias which arises from the selection of patients for treatment. The criteria which are recognized as guides for this selection are often also of a certain prognostic significance. A group consisting of treated patients only does not therefore warrant comparison with an untreated group which includes all types of cases indiscriminately. Bond (1954) again has tried to exclude this bias by comparing groups of schizophrenics, say all admissions of one year irrespective of whether they had treatment or not, with a similarly defined group observed

after the modern physical methods of treatment were known.

Owing to the foresight of Guttmann, Mayer-Gross, and Slater (1939) a similar opportunity offered itself to us. These authors reported a group of schizophrenic patients who were admitted to the Maudsley Hospital before the modern physical methods of treatment were used at that hospital. One of the stated reasons of their report was to have an "untreated" control group for future assessments of treatments. This has enabled us to compare an equivalent group of patients who were admitted to the same hospital after insulin coma and electro-convulsive therapy had been introduced.

We present a comparison of the outcome of the illness at the time of discharge from hospital of two groups of schizophrenic patients, of which one was not treated by either insulin coma or electro-convulsive therapy, whereas the other, while in all other ways comparable, includes patients who were so treated. Owing to the nature of this investigation the control group antedated the other by some 15 years. A follow-up study of the same case material is in preparation.

Material and Method

The 1934–35 Group.—This group, which will be called the "control group", was investigated by Guttmann and others (1939) and its characteristics were as follows:

(1) It consisted of all the schizophrenics discharged from the Maudsley Hospital between January 1, 1934, and December 31, 1935. (2) These patients had *prima facie* a favourable outlook owing to the admission policy of the hospital. (3) All patients were excluded who were over 46 years, the onset of whose illness antedated admission by more than 12 months, or in whose cases there was the slightest doubt as to the diagnosis.

(The case notes and protocols of these patients together with the most valuable comments by the investigators have been very generously made available to us for the purpose of this investigation.) The characteristics of the group together with the comparable data in the test group are set out in Table I.

From the control group we have rigorously excluded all patients in whom we were not satisfied that we were dealing with the first attack of the illness. This was done although careful comparison with the total group of patients originally described shows that the results were not materially altered.

The 1948–50 Group.—This group, which includes treated and untreated patients, will be referred to in this paper as the "test group". It includes all patients between the ages of 16 and 46 years who had no previous attacks, whose illness was of less than 12 months' duration, and who were admitted between January 1, 1948, and December 31, 1950, as in-patients to the Bethlem Royal Hospital and the Maudsley Hospital with a diagnosis of schizophrenia. They are in general comparable to the control group. From Table I it is apparent that the two groups differ only in composition with regard to diagnostic subgroups. This point and its implication will be discussed later.

As far as the treatment of this group is concerned, it falls into four classes. Those who were given (1) insulin coma therapy, (2) electro-convulsive therapy, (3) a combination of the two, and finally (4) those who had no such treatment. The precise composition of these groups is evident from Table III analysing the results.

The patients were admitted under the care of different clinicians on the staff of the hospital, who made the diagnosis and selected the patients for treatment. As far as the diagnosis is concerned this was scrutinized by the present authors before the

TABLE I

ANALYSIS OF COMPOSITION OF TEST AND CONTROL GROUPS COMPARED

	Control Group			Test Group		
	Male	Female	Total	Male	Female	Total
Patients .. .. No.	55	86	137	73	83	156
%	40	60	—	47	53	—
Average age and standard deviation	25·6±7	28·6±7·8	27·4±7·4	30·1±7·7	27·2±6·9	28·7±7·2
Average duration of stay in hospital (in months) ..	4·4	4·1	4·2	4·5	5·4	5
Average duration of illness from onset of symptoms to admission to hospital (in months)	5·2	4·7	4·9	5·6	4·7	5·1
Percentage composition of diagnostic subgroups:						
Hebephrenic			29			24
Paranoid schizophrenic			38			32
Catatonic schizophrenic			29			10
Atypical schizophrenic			4			34

case was included in this group. Only a negligible number, however, had to be rejected because of doubts as to the accuracy of diagnosis.

The Treatments

Insulin Coma Therapy.—This treatment was based on the technique originated by Sakel (1935). All patients in the treatment group who had insulin coma were treated in the Insulin Department of the Bethlem Royal Hospital. This department applied the treatment generally in the way described by Sargant and Slater (1954). The procedure remained uniform throughout the years under investigation. At every treatment deep coma is aimed at and maintained for 20 minutes. The average number of comas in this group was 33·2 with an S.D. of 7·8.

Electro-convulsive Therapy.—This was given with a Strauss-Macphail apparatus after modification by an intravenous injection of " pentothal ", 0·25 g. and C 10, 3 mg. The average number of treatments was 8 (S.D. 2·3). The method in general use in this hospital was described in detail by Davies and Lewis (1949).

Combined Therapy.—This method of treatment consisted in the application of E.C.T. during sopor : " interruption " followed at once by intravenous glucose.

Whether a patient was selected for treatment or not, and what type of treatment was given was decided by the clinician in charge of the case. Since the clinicians concerned were working quite independently of each other the methods of selection varied a great deal. Whether treatment is given depends of course on the general views held by the clinicians concerned. Some hold that where the prognosis is very poor the risks which the treatment involves are not justified by the small possibility of a remission, and their untreated group will therefore be mainly composed of patients with poor prognoses. Others will select those very cases for treatment as their chances of a spontaneous remission are small, and they should be given every chance of overcoming their illness. As the clinicians who were in charge of the present series include both schools of thought, our total group is naturally a very mixed one. The large variation in these views illustrates again the lack of accurate and precise knowledge on the efficiency of these methods of treatment. Other reasons for not giving treatment might be various, e.g., refusal of treatment by the patient, intercurrent illness, or such rapid improvement that treatment was not felt to be justified. The overall effect would seem to make a random selection of patients for various methods of treatment. Since the test group involves both treated and untreated patients the results will not be biased whatever the composition of the treated section of the group may be.

Scrutiny of Records

The present investigation consisted only in the scrutiny of case records made by the clinicians in charge of the cases. This applies equally to the test group and the control group. The authorities previously referred to have pointed to the difficulties which beset this type of investigation. We shall deal with the more important points raised by them in turn as they apply to this study.

Age and Sex.—As shown in Table I the two groups are comparable in these respects.

Duration of Illness.—Both groups only include patients with first attacks, and whose illness has lasted less than one year. Table I, giving more detailed information on the duration of the illness, shows that the two groups are very similar in this respect.

Diagnosis.—The question of the diagnosis of schizophrenia is a recurrent problem, but the difficulty is not so much that of the diagnosis of schizophrenia *per se*, as of the classification of the patients into the diagnostic subgroups and varieties of schizophrenia. It is well known that one and the same patient may, in the course of his illness, present a varying admixture of symptoms and signs at different times which may cause him to be diagnosed as hebephrenic, catatonic, paranoid schizophrenic etc. In the case of the control group four subgroups were distinguished—hebephrenic, catatonic, paranoid schizophrenic and paraphrenic. In 1948 to 1950 a diagnostic code was in use at the Bethlem Royal and Maudsley hospitals based on the " Revised Diagnostic List " taken from the " International Lists of Diseases and Causes of Death, Geneva 1947 ". This coding was used in the preparation of the Tables.

In the test series the hebephrenic and schizophrenia simplex cases were considered together since it is recognized that the differential diagnosis in the early stages is not easy (Curran and Guttmann, 1945). The percentage of the total is comparable in the two groups. The paranoid schizophrenic groups would seem to be strictly comparable in the two series. The atypical group in the test series includes paraphrenics, schizo-affective disorders, acute schizophrenic reactions, and otherwise atypical forms of schizophrenia. We are satisfied that the diagnosis of schizophrenia was a legitimate one in every case. The paraphrenic group of the control series falls readily into the atypical category.

There are, however, more atypical cases in the test series. The catatonic schizophrenics are fewer in the test than in the control group. This discrepancy is not easy to explain. It is possible that the atypical groups and the catatonic groups overlap to some extent. For example, the category "acute schizophrenic reaction" may fall into the atypical group or into the catatonic group, depending to some extent on the views of the individual clinician. It will be seen from Table I that the two series have comparable percentages if the catatonic and atypical cases are combined into one group, suggesting that this may be a correct explanation. The differences are emphasized here in view of the differences in the outcome. This will be discussed later.

Selection for Admission.—The two groups have been admitted to the same hospital with the admission policy unchanged. The Bethlem Royal and Maudsley Hospital being a teaching hospital does of course select its admissions to a certain extent. Only voluntary patients are being admitted, and patients with chronic illnesses and very bad prognoses are mostly excluded. As far as duration of illness is concerned we have only included patients with less than one year's history. We have set out to compare a largely treated group of schizophrenic patients with an untreated group; the selection methods of the hospital will not affect the results provided they have not changed. Because of this selection the findings in these groups may not, of course, be applicable to schizophrenic patients in general, but since the physical methods of treatment are usually thought to be most effective in "fresh" cases, the results in the two groups which consist of that type of case should be of particular interest.

Selection for Treatment.—We have already pointed out that the indications used for selection for treatment as such and for the different types of treatment varied widely. The treated and untreated sections within the test group are not at all comparable. Nor are the treated patients alone comparable with the control group. We do not know the exact criteria of selection which applied to each patient. It is therefore possible that the treated section would tend to be biased by containing more of a certain type of patient than the untreated section. In order to avoid this source of error which beset many previous investigations, we have not compared the outcome of the treated patients alone but have taken *all* schizophrenic patients who have passed through the hospital within the stated period. If treatment by the physical methods has any benefit the test group should on the whole show a better outcome than the control group.

The classification of outcomes in the test group was standardized in the following categories: (1) Recovered, (2) much improved, (3) improved, (4) slightly improved, (5) unchanged, (6) worse, (7) dead, (8) suicide. The assessment was that of the clinician in charge of the case. In the control group the assessment of the result on discharge was stated in comparable categories, and there was no difficulty in translating these into the code used above, which had been adopted in the hospital at a later date.

Results and Discussion

Effectiveness of Physical Treatment.—As a first step we shall attempt to evaluate the effect of physical treatment on schizophrenia without any reference to the particular type of treatment. As is well known the assessment of the degree of improvement is very difficult and always subjective to a certain extent. In order to simplify the assessment we are in the first instance only comparing "improved" with "not improved", ignoring for the moment the degree of improvement. "Improved" includes the categories recovered, much improved, improved, and slightly improved; "not improved" includes the categories unchanged, worse, and dead. Table II shows the outcome on discharge from hospital in the test and control groups for comparison.

If the test and control groups are compared as a whole, ignoring for the moment the question of treatment within the test group, the relevant figures are for the control group: improved, 50 cases (35%), not improved, 87 cases (65%); for the test group: improved, 107 cases (68%), not improved, 49 cases (32%). This difference is highly significant statistically ($P<0.01$). The outcome in the test group is much better than in the control group. Since the two groups are in other respects comparable this would strongly suggest that the difference is due to physical treatment. If that were so the same trend should be apparent within the test group itself if the treated and untreated sections were compared. Table II shows the results when

TABLE II
COMPARISON OF CONTROL GROUP WITH TREATED AND UNTREATED SECTIONS OF THE TEST GROUP

	Test Group		Control Group
	Treated Section	Untreated Section	
	Number of Patients	Number of Patients	Number of Patients
Improved ..	80 (78%)	27 (51%)	50 (35%)
Not improved ..	23 (22%)	26 (49%)	87 (65%)
Total ..	103	53	137

the test group is broken down in this way. Comparing these two sections there is a considerable and significant difference between the treated and untreated. The results in the untreated section, however, are better than in the control group and this difference is significant at the 5% level. This in itself casts some doubt on the absolute validity of the first conclusion. Were treatment alone responsible for the difference between the two series, it would be expected that the untreated section would show results similar to or worse than the controls. This is not the case, and the untreated section, while not so good as the treated section, has still done better than the control group. The suggestion is that factors other than treatment must also play a part in the apparent improvement; for example, the case material may have been in some respects dissimilar. To investigate this point the same comparisons were made with the material broken down into the various diagnostic subgroups.

Hebephrenic Group.—At once it is evident (Tables III and IV) that as far as the hebephrenics are concerned the figures in the test group and control group are similar. The control group has 43% improved compared with 45% improved for the test group. There is, however, a distinct difference when the treated and untreated sections of the test group on the one hand, and the control group on the other hand, are compared. The untreated hebephrenics did very much worse than the control group, and the treated hebephrenics better by 19%. This suggests that in fact a better prognostic group was selected for treatment and a worse left untreated. The conclusion from this is that physical treatments did not materially affect the outcome in this group of hebephrenics.

Paranoid Schizophrenic Subgroup.—In the case of the paranoid schizophrenic group, the outcome of the test group as a whole is superior to the control group (Tables III and IV). Forty-seven per cent. of the control group improved compared with 63% of the test group. The outcome of the untreated section of the test group of paranoid schizophrenics is similar to that of the control group, while that of the treated section is superior to both. In this case it seems reasonable to suppose that the improvement is due to the physical treatment, although the evidence is not conclusive.

Catatonic and Atypical Subgroups.—Lastly there are the catatonic and atypical groups which can be dealt with together as the diagnoses probably overlap and as the figures in the two groups show similar trends (Tables III and IV). We find that the test group as a whole with 79% improved did very much better than the control group with 31% improved. In fact the difference is more striking than in either of the other diagnostic subgroups. If, however, the treated and untreated sections of

TABLE III

COMPARISON OF DEGREE OF IMPROVEMENT IN DIAGNOSTIC SUBGROUPS OF CONTROL AND TEST GROUPS, AND IN TREATED AND UNTREATED SECTIONS OF THE LATTER

	Hebephrenic Schizophrenia			Paranoid Schizophrenia			Combined Catatonic and Atypical Schizophrenia		
	Control Cases 40	Test		Control Cases 52	Test		Control Cases 45	Test	
		Treated Cases 26	Untreated Cases 11		Treated Cases 30	Untreated Cases 19		Treated Cases 46	Untreated Cases 23
Improved (%)	43	62	9	37	80	37	31	80	78
Not improved (%)	57	38	91	63	20	63	69	20	22

TABLE IV

COMPARISON OF OUTCOME OF TEST AND CONTROL GROUPS IN DETAIL

	Hebephrenic		Paranoid Schizophrenic		Catatonic and Atypical Schizophrenic	
	Control Cases 40 (%)	Test Cases 37 (%)	Control Cases 52 (%)	Test Cases 49 (%)	Control Cases 45 (%)	Test Cases 69 (%)
1. Recovered	8	13	10	6	2	33
2. Much improved	2	11	4	31	2	22
3. Improved	23	5	19	12	27	14
4. Slightly improved	10	16	4	14	—	10
5. No change	57	51	59	37	67	18
6. Worse	—	3	2	—	2	3
7. Died	—	—	2	—	—	—

the test group are compared (Table III) the expected difference is not found. Instead it will be seen that the outcome in the untreated section is very much the same as that in the treated section. Again we are driven to the conclusion that factors other than treatment must be involved to account for the differences in the two groups.

The final conclusion is therefore that it is only the paranoid schizophrenic group that seems to show a large response to physical treatment. There is no evidence, in differences of duration of illness, mean age, or sex distribution, that the paranoid schizophrenic group were more favoured in the test than in the control series, and if factors other than physical treatment were operative, they are not immediately apparent.

Effectiveness of Different Types of Physical Treatment.—It will be seen from Table V that by far the larger proportion of patients had insulin therapy alone or combined with E.C.T. A minority had E.C.T. alone. As far as these small figures permit any conclusion it would seem that there is little to choose between the various methods. Since, however, the paranoid schizophrenic group shows the most convincing response to treatment we have analysed this group further as regards types of treatment. The insulin-treated section is numerically by far the largest (23 of 32 treated) so that the other forms of treatment are not likely to have affected the results appreciably, Of the 23 insulin-treated cases, 22 showed improvement. The effectiveness of treatment in this group would therefore appear to be due to insulin coma therapy and not E.C.T. or the combined insulin and E.C.T. The comparative value of these methods, however, cannot be assessed from our figures with any degree of confidence.

TABLE V

NUMBER OF PATIENTS RECEIVING ONE OR OTHER OF VARIOUS TYPES OF PHYSICAL TREATMENTS WITH THE RESULTS IN THE TEST GROUP

	Insulin Coma Therapy	Combined Insulin Coma and Electro-convulsive Therapy	Electro-convulsive Therapy	No Treatment
	Number of Patients	Number of Patients	Number of Patients	Number of Patients
Improved	48 (81%)	20 (74%)	12 (71%)	27 (51%)
Not improved ..	11 (19%)	7 (26%)	5 (29%)	26 (49%)
Total ..	59 (38%)	27 (17%)	17 (11%)	53 (34%)

Assessment of the Results.—The better results apparent in the paranoid schizophrenic group may not be due to the physiological effects of insulin. It has been pointed out before that the care, attention, and optimistic therapeutic environment of a busy insulin unit may in themselves be conducive to the improvement. It has even been asserted that this is the only cause for any apparent improvement. The fact that the other diagnostic subgroups did not generally respond in the same favourable way, although exposed to the same régime, tends to cast doubt on such a notion. It can, however, be argued that the different psychopathology of the paranoid schizophrenic may make him specially susceptible to the particular measures employed in an insulin unit. The present investigation cannot answer this question. A different type of experiment would be necessary to test such a hypothesis.

In the presentation of results so far, no attention has been paid to possible qualitative differences in the groups as regards outcome. The varying degrees of improvement have been represented as a comprehensive single figure. Table IV shows how the groups compare with regard to the more detailed description of the outcome. It will be seen that the trends described hitherto are essentially unchanged. A more detailed breakdown of the figures of Table IV, which is not presented here in full, suggests that there is some advantage to the test group hebephrenics as regards total recovery, which could be attributed to treatment. Similarly, in the catatonic and atypical subgroup of the test group, the treated section has an 11% advantage over the untreated as regards " total recovery " (37% to 26%) and a 7% advantage as regards " much improved " (24% to 17%). However, in the other categories of " improved " and " slightly improved ", the untreated section is superior.

It is difficult to draw precise conclusions from these figures, and the question must be left open.

There remains the puzzling finding that the catatonic and atypical group seem to have a much better short-term prognosis in the test group than in the control group, and that independently of whether they had treatment or not. A possible explanation could be that the nature of the illness has changed in the course of the years (Bourne, 1953). We must state that perusal of the case histories of the control and test groups did not impress us by any marked difference in symptomatology. Furthermore in whatever way the test group may differ from the control group, the difference is maintained consistently in each of the three years 1948, 1949, and 1950. Harris and Norris (1954) showed in a very interesting study that mental hospital populations have changed in the course of time. This change is closely linked

with the major alteration in legislation referring to mental illness due to the introduction of the Mental Treatment Act 1930, and they concluded that this Act brought a different type of patient into the mental hospital, with better prognosis. As far as the Maudsley Hospital is concerned this factor can only be thought of as applying in a very limited way, since, as a teaching hospital, it has always admitted voluntary patients, the majority of whom had a good prognosis. Another factor which may be of great importance is the therapeutic optimism in psychiatric hospitals with its effect on the doctors and other staff and secondarily on the patients. These theories could be tested by comparing similar figures from other hospitals for suitably selected periods. As yet they can only be accepted as purely speculative though not unlikely.

Summary

The outcome of the illness at the time of discharge from hospital of two groups of schizophrenic patients is compared. One group was observed before, the other after, the introduction of the modern physical methods of treatment, namely electro-convulsive therapy (E.C.T.) and insulin coma therapy. The two groups are comparable in most relevant respects. They are designated the control group and the test group respectively.

The test group does better as a whole than the control group, but further analysis suggests that factors other than the physical methods of treatment may be concerned.

Treatment by insulin coma and E.C.T. seems to benefit the group of paranoid schizophrenics most convincingly, although even that is not conclusive.

An additional finding is that the short-term prognosis of catatonic and atypical schizophrenia appears to have undergone a change for the better. This cannot be attributed with certainty to the insulin coma or electro-convulsive therapy.

Possible explanations for this change in prognosis are discussed.

Our thanks are due to Professor A. J. Lewis for permission to carry out the investigation and helpful criticism, and to Dr. W. Mayer-Gross and Dr. E. T. O. Slater for permission to use the protocols of the control group. We should also like to thank Dr. Slater for helpful criticism.

References

Bond, E. D. (1954). *Amer. J. Psychiat.*, **110**, 561.
Bourne, H. (1953). *Lancet*, **2**, 964.
Cossa, P., Bougeant, H., and Lombard, A. (1948). *Ann. méd.-psychol.*, **106**, (2), 24.
Curran, D., and Guttmann, E. (1945). *Psychological Medicine*, 2nd ed. Livingstone, Edinburgh.
David, H. P. (1954). *Amer. J. Psychiat.*, **110**, 774.
Davies, D. L., and Lewis, A. J. (1949). *Lancet*, **1**, 775.
Garmany, G. (1946). *J. ment. Sci.*, **92**, 801.
Gottlieb, J. S., and Huston, P. E. (1951). *J. nerv. ment. Dis.*, 113, 237.
Guttmann, E., Mayer-Gross, W., and Slater, E. T. O. (1939). *Journal of Neurology and Psychiatry*, **2**, 25.
Harris, A., and Norris, V. (1954). *J. ment. Sci.*, **100**, 727.
Hughes, J. (1953). In *Psychiatric Treatment. Res. Publ. Ass. nerv. ment. Dis.*, **31**, 193.
Kalinowsky, L. B., and Hoch, P. H. (1952). *Shock Treatments, Psychosurgery and Other Somatic Treatments in Psychiatry*, 2nd ed., p. 30. Grune and Stratton, New York.
——, Worthing, H. J., (1943). *Psychiat. Quart.*, **17**, 144.
Lewis, A. (1945). *Brit. med. Bull.*, **3**, 22.
Malamud, W., and Render, N. (1939). *Amer. J. Psychiat.*, 95, 1039.
Mayer-Gross, W., Slater, E., and Roth, M. (1954). *Clinical Psychiatry*, p. 286. Cassell, London.
Meduna, L. von (1935). *Z. ges. Neurol. Psychiat.*, **152**, 235.
Sakel, M. (1935). *Neue Behandlungsmethode der Schizophrenie*. Perles, Vienna and Leipzig.
Sargant, W., and Slater, E. (1954). *An Introduction to Physical Methods of Treatment in Psychiatry*, 3rd ed. Livingstone, Edinburgh.
Silverman, D. (1941). *Psychiat. Quart.*, **15**, 477.
West, F. H., Bond, E. D., Shurley, J. T., and Meyers, C. D. (1955). *Amer. J. Psychiat.*, **111**, 583.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 137.

SODIUM AMYTAL AND BEHAVIOUR IN NEUROTIC SUBJECTS

BY

S. G. LAVERTY and C. M. FRANKS

From the Institute of Psychiatry (Maudsley Hospital), University of London

Sodium amytal is a barbiturate drug which has been used for some 25 years as a sedative, narcotic, and anticonvulsant. Data concerning its action and the action of structurally similar moderate-duration barbiturates such as " dial " and " nembutal ", suggest that it has both central and peripheral effects upon the nervous system. It has been shown to alter the normal electroencephalogram producing high-voltage fast activity in doses of about 3 grains intravenously, and slow activity in anaesthetic doses (Brazier and Finesinger, 1945). Clinically, by mouth or injection, in adequate dosage sodium amytal produces drowsiness and sleep (Council on Pharmacy and Chemistry, 1931), and small doses intravenously have been described as producing increased communicativeness and feelings of well-being in normal subjects (Lindemann, 1932). In anxious subjects there is frequently an alleviation of anxiety (Sargant and Slater, 1954), and in neurotic subjects communicativeness and unrestrained emotional expression may reach the point of abreaction (Horsley, 1943; Ripley and Wolf, 1947; Mallinson, 1940). Abstinence from regular use of the drug may be associated with withdrawal symptoms which include insomnia, restlessness, epileptic seizures, and psychotic states, generally of a delirious type (Wikler, 1953). These phenomena have been interpreted as indicating that amytal depresses cerebral mechanisms, particularly those functions mediated by the cerebral cortex. But the influence of barbiturates on the nervous system has been differently interpreted according to the stage of anaesthesia obtained (Brazier, 1954).

Adrian (1941) has shown in a variety of experimental animals that dial and nembutal anaesthesia alters the cortical components of the electrical activity recorded from that structure, and reduces the tendency for afferent stimuli to produce excitation in appropriate parts of the cortex. It also reduces the tendency for such excitation, when it does occur, to spread into the neighbouring cortex.

Experiments of Masserman (1938) in the cat suggested that amytal depresses sympathetic and emotional mimetic activity resulting from faradic stimulation of the hypothalamus. It was suggested that this interference was at the level of the hypothalamus. Subsequently, Trethewie (1953) has shown that nembutal inhibits the output of adrenaline from the sympathetic nerve endings and from the adrenal medulla, and that this is a peripheral effect situated principally at the level of the autonomic ganglion cell. The interference with sympathetic nervous functions by amytal is probably sited peripherally at this level also.

Sodium amytal has been described as " deconditioning " subjects prone to anxiety in specific anxiety-provoking situations (Sargant and Slater, 1954), and it has been found to abolish conditioned fear responses in kittens (Bailey and Miller, 1952). The present authors (Franks and Laverty, 1955) have shown elsewhere that amytal administered intravenously tends to depress both the acquisition and the resistance to extinction of eyelid conditioned responses in dysthymic subjects. (" Dysthymic " is a term used by Eysenck (1947) to describe those introverted neurotics generally diagnosed as suffering from anxiety states, obsessive compulsions, or reactive depression.) In the same paper it has also been shown that amytal apparently increases extroversion, as measured by Guilford's questionnaire (Guilford, 1940).

The present paper, which must be regarded as a pilot study only, is concerned with more general aspects of behaviour and personality changes observed during and immediately after the conditioning experiment referred to above.

Subjects

Sixteen subjects suffering from neurotic illness and regarded as free from psychotic traits, organic brain damage, and subnormal intelligence were selected on the basis of their possessing personalities of a predominantly introverted type. This selection was made on the evidence provided by their case records, and an interview at which their cooperation in the investigation was invited. They were told that the purpose of the investigation was to discover whether a certain drug (whose name they were not told) would have a relaxing action upon them. Seven subjects were male, nine female. Ages ranged from 17 to 46 years.

Treatments

To estimate the influence of the drug four types of treatment were employed : (A) A larger dose of sodium amytal ; (a) a smaller dose ; (P) a placebo injection of sterile water ; (N) no injection.

The choice of these four treatments was arrived at as follows. It is well known to anaesthetists and other workers using drugs of the barbiturate series that there is a wide variation in the susceptibility of individuals to these drugs. For example, Goodman and Gilman (1941) conclude that " when barbiturates are injected intravenously it is difficult to judge in advance the amount to be given . . . reliance cannot be placed on fixed doses based on age and weight . . . individuals vary in their response ".

The mental state may in some cases influence the dosage requirements. Manic patients can tolerate extremely high doses and patients suffering from organic brain damage appear to be rendered unconscious by smaller doses of amytal than psychiatric patients suffering from the functional psychoses and from psychoneuroses (Thorner, 1935). As has been suggested by Franks (1954) this may be explained in terms of Pavlov's concepts of cortical inhibition and excitation. Patients with brain injuries may be regarded as possessing more than the normal amount of inhibition and would therefore require less of a cortically inhibiting drug such as sodium amytal to induce an inhibitory phenomenon such as sleep. Intravenous doses of 1·5 grains of sodium amytal have been regarded as reducing nervous tension in neurotic subjects (Susselman, Feldman, and Barrera, 1946). Doses of up to 7½ grains intravenously have been used to obtain the state of drowsiness deemed most suitable for procuring abreaction (Mallinson, 1940).

Before selecting the dosage of sodium amytal for the present experiment some preliminary trials were carried out on the type of subject to be used. There appeared to be some positive relation between the degree of manifest anxiety and the dosage required for its relief, and a tendency for physically heavier patients to tolerate a larger dose without drowsiness. Two doses were selected, a larger dose (A) of ½ grain per stone body weight, and a smaller dose (a), which was always 2 grains less than the larger as calculated for each subject. This gave a dosage range varying from 4 to 6 grains for the larger dose and from 2 to 4 grains for the smaller. It was expected that these differences in dosage might be reflected in the results obtained. Clinically these doses would seem to work satisfactorily ; no subjects are made too drowsy to participate and yet all appeared clinically to be influenced by the drug.

Placebo (P) injections (10 ml. sterile water) were given intravenously in place of the drug in a quarter of the tests, and no injection (N) in a further quarter. It is unnecessary to stress the importance of using a placebo in such drug trials, except to say that comparison with an inert substance is particularly essential when drugs which may influence suggestibility are employed. Eysenck and Rees (1945) have shown that sodium amytal under certain conditions increases suggestibility and Lewis (1941) has called attention to the possible influence of suggestion in procuring therapeutic results by barbiturate abreaction.

Experimental Design

Since there are four different treatments it would have been preferable if each subject were given all four treatments so that full comparisons within each subject could be made. For administrative reasons each subject could be seen only twice. This made the experimental design a more complicated one. It is possible to construct a " balanced design " so that each subject receives two different treatments and yet all treatment combinations are covered by using only six subjects (a–a ; A–P ; A–N ; a–P ; a–N ; P–N). However, since the order of treatment may be important it is necessary to repeat each of these six combinations on a different subject but in the reverse temporal order, e.g., N–A and A–N. The 12 patients were allocated to these 12 treatment combinations by reference to a table of random numbers.

In addition it was thought worth while at this pilot stage to investigate the consequences of giving the same treatment upon both occasions. Therefore four subjects, also selected at random from the initial 16, were tested with the treatment combinations A–A, a–a, P–P, and N–N. The interval between test and retest was five to seven days.

Procedure

The subject was taken to a room adjacent to the testing room and requested to rest on a couch for a few minutes while the injection was prepared. Sodium amytal, 7½ grains, was dissolved in 15 ml. of sterile water giving a solution containing 1 gr./2 ml. The appropriate amount of the solution was injected intravenously in the right arm at a rate of 1 grain (2 ml.) per minute. After the needle was withdrawn the pulse was taken and the subject was requested to sit up. After three minutes the subject walked a few yards to the soundproof conditioning laboratory (Franks, 1955). Here he was seated comfortably and fitted with the apparatus necessary for eyelid conditioning. This consisted of a pair of padded earphones, a pair of plain glass spectacles for deliverance of a mild (65 mm. of mercury) air puff and for housing a recording photo-electric cell. The subject was seated at a booth, so situated that his field of vision was confined largely to the walls of this booth.

The same procedure was adopted for the placebo injection, except that sterile water was used. For the " no injection " treatment the subject was told to rest for approximately the same time as was normally taken up by the other treatment procedures. At all times every possible care was taken to ensure that the subject was given no indication of which treatment he had received or was about to receive except in so far as he was naturally aware that he was receiving no injection whatsoever.

Seven minutes after the injection was terminated the conditioning procedure was begun. This followed a routine pattern (Franks, 1956) and lasted approximately 30 minutes. During this time a detailed clinical observation of the subject's behaviour was made by one of the experimenters. Each subject was then questioned as to

his subjective feelings and impressions immediately after the injection and during the conditioning and clinical behaviour study.

Finally the subject was asked to sort several questionnaire scales of Guilford (1940) and the Maudsley Medical Questionnaire. Included in the Guilford scales were scales S (social introversion), D (depression), C (cycloid disposition), and R (rhathymia). However, there is good evidence (Hildebrand, 1953) to suggest that D and C are largely measures of a personality factor of general neuroticism and R is largely a measure of extroversion. It has been shown by Eysenck (1953) that neuroticism and introversion-extroversion are two mutually orthogonal dimensions of personality. Dysthymic neurotics have a high score on neuroticism and on the introverted end of the introversion-extroversion dimension ; hysteric and psychopathic neurotics have a high score on neuroticism and on the extroverted end of the introversion-extroversion dimension.) Unlike the standard procedure suggested by Guilford, each item was printed on a separate card. The subject was then instructed to " post " each card into one of three boxes marked "Yes", "?", and "No" respectively. The Maudsley Medical Questionnaire (M.M.Q.) is a scale of 58 items consisting of 40 " neurotic " items and 18 lie scale items. There is good evidence (Hildebrand, 1953 ; Eysenck, 1952) to suggest that, given adequate subject motivation, the M.M.Q. is a reasonably good measure of neuroticism. This scale was administered in a manner similar to the previous ones except that only two boxes were used labelled "True" and "False" respectively.

Clinical Observations of Behaviour

During the conditioning experiment the subject is seated quietly in a chair, the head supported by a padded head-rest, the arms lying in the lap, the feet resting on a footstool. The subject has been instructed that he has nothing to do except relax and look at a low-powered red light whenever it goes on. Under these conditions it might be expected that whatever movements occurred would be related to discomfort, anxiety, or tension experienced by the subject. Preliminary observations led us to expect three groups of movements to occur with some regularity. These were : (1) Movements of the general somatic musculature ; of the head or limbs, or shifting of the whole body. These were generally slow, stretching movements or simple shifts in posture commonly shown by people constrained to sit still for any length of time. In addition there were observed more rapid movements, foot-tapping and finger-tapping (in one case each), and a sudden jerk of the head in response to the air puff impinging on the eye. This latter movement usually occurred in response to the first two or three puffs only and disappeared thereafter. (2) Respiratory movements ; deep breathing (periodic hyperventilation), coughing, clearing the throat, yawning. (3) Movements of the mouth ; swallowing, wetting the lips.

The observer sat behind and to the right of the subject, who never appeared to be aware of being observed. In this position a profile of the subject, which included the mouth, neck, supraclavicular region, and arm and leg on the right side, was easily observed.

Under the somewhat constraining conditions of the experiment the movements observed were generally sufficiently isolated, definite, and infrequent to make the accurate recording of them both feasible and straightforward. Attention was focused on the areas (neck and supraclavicular) where breathing and swallowing were observed. It was the rule to find subjects drawing an occasional deep breath or sometimes audibly sighing during otherwise quiet breathing. Movements of the head, limbs of the right side, and general shifts of the whole body in the chair were recorded when they occurred. Frequently a sequence of deep breathing, swallowing, and general shifting was observed.

Observations were made for periods of four minutes followed by one minute's rest for the observer. All movements of the patient as described above were recorded during these four-minute periods. After five such periods the conditioning experiment was nearly ended and no further observations were recorded.

Analysis of Data

The analysis of variance technique was used, modified in the manner recommended by Cochran and Cox (1950). For each measure the average treatment effect is the straightforward average for each treatment. This has then to be adjusted to allow for the fact that any one person has only received two of the four possible treatments, the method of adjustment being that followed by Cochran and Cox. It is these adjusted treatment effects (H) which are used for t tests of significance whenever the analysis of variance yields a significant F ratio. The appropriate error variance for the t tests (Cochran and Cox, 1950) is given by $\frac{1}{2}$ (residual error variance in the analysis of variance).

The results for the four persons tested A–A, a–a, P–P, and N–N were treated separately from the main data, the analysis being confined (since this is a pilot study) to a simple examination of the data. Finally the raw scores for the clinical behaviour measures were correlated.

Results

Movements.—As can be seen from an examination of Table I the result of adjusting the treatment means is that sometimes the adjusted treatment mean (H) is negative. Analysis of variance of each movement gives no significant F ratios for the treatment effects with the exception of deep breathing where the treatment effect F ratio is significant at the 1% level ($F = 34{\cdot}2$, d.f. $= 3$ and 8). When t tests are carried out on the differences between the adjusted deep breathing means for different treatments it is found that sodium amytal (A, a) significantly reduces the number of deep breaths ($P<0{\cdot}05\%$). There is no significant difference between the number of deep breaths produced with treatments P, i.e., using a placebo, and N, i.e., using no drug, which fail to reveal any

TABLE I

AVERAGE NUMBER (ADJUSTED) OF MOVEMENTS FOR EACH TREATMENT USING ADJUSTED TREATMENT MEANS (H)

Movement	Treatment A	Treatment a	Treatment P	Treatment N
Head	0·25	1·63	1·88	1·76
Arm on right side	0·16	0·79	1·04	1·17
Leg on right side	0·75	0·12	1·25	0·88
General shifting of body ..	−0·17	1·84	0·96	1·21
Cough	−0·54	0·33	1·96	2·09
Deep breath..	−0·50	2·00	7·26	6·76
Swallowing	0·83	1·08	7·84	6·09
Mouth	Number of recorded movements too low for consideration			
Total movements ..	1·13	7·38	23·89	20·64

"suggestion effects" as far as deep breathing is concerned. The larger dose of amytal (A) produces significantly fewer deep breaths than the smaller dose (a) ($P < 2{\cdot}5\%$).

Analysis of variance of the total number of movements yields a treatment effect F ratio significant at the 5% level. t Tests show that the total number of movements for the drug treatments is significantly less ($P<1\%$) than the total number of movements when no drug is given. As before, no significant differences were found for the total number of movements for the two treatments P and N.

The movements of the four subjects given the same treatments at test and retest are approximately in agreement with these findings. Thus the average number of movements of all kinds for the two subjects receiving amytal (A and a) is 14, and the average number of movements for the two subjects not receiving amytal (P and N) is 29.

As far as possible, i.e., when the distribution of the data and the lack of zero numbers allowed, the Pearson product moment intercorrelations between the various movement scores were calculated (Table II).

TABLE II

INTERCORRELATIONS BETWEEN MOVEMENT MEASURES USING ADJUSTED TREATMENT MEANS (H)

Correlation Between	H.RA	H.RL	H.GS	RA.RL	RA.GS	RL.GS	DB.S
r	0·37	0·12	0·85	0·32	0·33	0·57	0·44

RA right arm, RL right leg, GS general shifting of body, DB deep breathing, S swallowing, H head.

Although only two of the above correlations are statistically significant (using a two-tailed test r must be 0·50 for significance at the 5% level) they are all positive and suggest some agreement between the various measures. Subjects who score high/low on one measure tend to score high/low on other measures.

The Personality Questionnaires.—Analysis of variance failed to reveal any significant treatment effects or tendencies for the measures of neuroticism used (Guilford's D and C scales and the M.M.Q.). Neither is there any significant treatment F ratio for the Lie scale. Also no consistent trends are observable for any of these measures.

Table III gives the adjusted treatment means (H) for the total number of cards put in the "Yes" box and for the total number of cards put in the "?" box.

TABLE III

TOTAL NUMBER OF QUESTIONNAIRE ITEMS ANSWERED "YES" OR "?"

ADJUSTED TREAMENT MEANS (H)

Answer	Treatment A	Treatment a	Treatment P	Treatment N
Yes	124·6	120·2	102·7	99·3
?	3·9	6·0	15·3	13·9

Analysis of variance shows that the test-retest F ratio is insignificant for both measures. The treatment effect F ratio is significant at the 1% level for the number of cards answered "Yes" but insignificant for the number of cards answered "?". t Tests show that, irrespective of which dose of sodium amytal is injected, the number of cards answered "Yes" is significantly ($P < 1\%$) greater than when the P or N treatment is used. There is no significant difference between the "Yes" scores for P and N. There would also seem to be an insignificant but consistent tendency for sodium amytal to reduce the number of cards answered "?". These findings are in agreement with the results obtained for the four subjects given the same test and retest treatment. Thus the average "Yes" score for subjects receiving amytal is 121 whereas the average "Yes" score for subjects not receiving amytal is 107. Similarly the average "?" scores are 5 and 10 respectively.

Responses to Verbal Questions.—(1) All subjects were asked, "How did you feel after the injection?" or "How did you feel?", if treatment N was given.

Some of the responses given in answer to these questions are as follows. (In evaluating the replies it should be remembered that for some of the subjects the question was being asked for the second time, i.e., during the second session and that they had therefore received one of the four treatments at the first session.)

Subjects Receiving Larger Dose of Drug (A)

I felt better—the tight feeling in my stomach has gone.
I felt drowsy, the same as last time.
It's escape—very relaxed—as if I'd had a good drink.
Very sleepy.
I never felt so pleasantly dreamy in my life.

Subjects Receiving Larger Dose of Drug (A)--cont.

I was drowsy—pleasant though—like being drunk.
A lovely feeling—slightly dizzy.
Why should I worry—I've had a row with my wife—but I don't care—it's all over.

Subjects Receiving Smaller Dose of Drug (a)

Felt rather sleepy—stopped worrying about anything. I feel good now.
I feel sleepy—in a dream almost.
A bit swimming—like one over the eight.
The fluttering in my stomach has gone—but it went to my head too—I was afraid someone would take advantage of me.
Eased my nerves—I feel quite composed.
Relaxed me like last time—what is it?
Felt relaxed—sort of couldn't care less.
It's nice—but it's a little hard having to concentrate when you want to relax.
I feel as if I'd had a few beers—a happy feeling.

Subjects Receiving Placebo (P)

I'm not relaxed like I was last time—don't feel relaxed at all.
It was a bit of a strain—I didn't feel any different really.
Felt no difference—was worrying about possibility of getting evening appointments.
No effect—it didn't seem to work on me.
Couldn't keep my mind still.
Last time I was thinking about all different things—this time my mind was just a blank.
This time my left side went all stiff—I didn't feel happy like I did before.
I was worried if the effect would last—thought I might attack someone while I was drugged. Felt upset about that.

Subjects Receiving No Injection (N)

This time I felt restless, last time I didn't mind, this time I felt like blinking more.
I was all right—uncomfortable having to sit still so long.
All right—not sorry it's the last one.
I don't recall feeling any different from usual.
I'm afraid I wasn't relaxed enough for you.
I was thinking too much—it was like the 9 o'clock news.
Not like last time—hardly remember that—I felt the puffs more this time.
It was better than I expected.

In general, subjects receiving sodium amytal tended to report pleasant feelings of relaxation, drowsiness, relief from worry or somatic discomfort, pleasant and happy feelings, slight dizziness, and difficulty in concentration. Subjects receiving the placebo injection or no injection tended to report no change in their feelings and commented upon their general feelings of discomfort.

(2) All subjects were asked, " How did the air puff feel? " Subjects receiving amytal (A or a) tended to report the air puff stimulus as bearable (11 subjects), not unpleasant (12 subjects), much less unpleasant than last time, less strong than last time, negligible (each one subject).

Subjects receiving the placebo injection (P) tended to report the air puff stimulus as slightly stronger than before, " made you jump this time, not at all before ", slightly unpleasant. Only five subjects reported the air puff as being bearable.

Subjects receiving no injection (N) reported the air puff stimulus as being stronger than before, uncomfortable, rather unpleasant. Only four subjects reported the air puff as being bearable or " not bad ".

(3) All subjects were asked, " Was it hard to sit still? " Subjects receiving amytal (A or a) answered "No" (14 subjects), "Yes" (one subject), "a little" (one subject). Of the subjects receiving a placebo or no injection (P or N), only eight answered "No" and six answered "Yes".

(4) All subjects were asked, " Did it seem a very long time that you sat there? " (actually about half an hour). Subjects receiving amytal (A or a) replied "No" in 10 cases. Other answers were "very quick, really ", "only a few minutes", " 10 minutes or so ", " over very quickly ", " not long ". No one answered "Yes".

Subjects receiving a placebo or no injection (P or N) reported " Yes" in six cases. Nine subjects replied "No".

Discussion

Movements.—The number of movements observed clinically under treatment P (placebo) was never significantly different from that observed under treatment N (no injection), neither were any trends apparent. In those cases where drug treatments were employed the total number of movements was significantly fewer than when no drugs were used.

Assuming that changes associated with the administration of the drug (and absent when a placebo was given) can be attributed to its action the following conclusions are permissible. (1) Sodium amytal, as administered in the present study significantly reduces the total number of movements observed. (2) Sodium amytal significantly reduces deep breathing (periodic hyperventilation). This reduction is very marked and in some cases the deep breathing was abolished completely during the period of observation. (3) Although the differences are not significant apart from deep breathing, for each of the eight individual movements the two drug treatments seem to produce fewer movements than the two treatments not using drugs (with one exception). (4) The increase in dose of 2 grains from the smaller (a) to the larger (A) dose of amytal produces a significant further reduction in movement only in the case of deep breathing.

A tentative interpretation of these findings required consideration of other information. Brazier (1954), in a detailed review of the effects of

barbiturates on the nervous system, suggested that the first stage of barbiturate anaesthesia (before sleep is induced) is attributable to the action of these drugs on the cerebral cortex alone. She relates effects found in deeper anaesthesia to the influences of the drug on the sub-cortical non-specific sensory systems.

> "High-voltage fast activity is characteristic of this first stage of barbiturate anaesthesia, and there appears to be differential activity on the part of different cortical areas. Fast waves of the orbital cortex appear to be independent of those of the cortex at the convexity. It seems reasonable to deduce that barbiturate at this stage acts directly on the cortical cells, and that the cortex is not being paced into any kind of synchrony from below, although the drug may well be having the same type of independent effect on neuronal groups subcortically."

The effect of the dosage of sodium amytal used in the present study corresponds to the first stage of barbiturate anaesthesia. The subject's behaviour is affected but sleep is not induced, and there is practically a normal degree of control of voluntary movements. The dosage employed (2 to 6 grains) is that at which fast activity could be expected in the E.E.G.

The reduction of movements may be understood as a failure of sensory stimuli to produce a spread of electrical activity through the cortex, even when producing a sharp localized cortical response, as described by Adrian (1941) in a variety of experimental animals under dial anaesthesia.

Periodic hyperventilation in neurotics has been regarded as of cortical origin since it disappears in sleep (Mudd, 1925). In the present study it has been found that such respiratory movements appear to be reduced to a greater extent by sodium amytal than those movements affecting the general muscular posture of the head, body, and limbs. Now respiratory movements are represented on the orbital surface of the cortex and muscular movements on the convexity surface. Therefore the differential influence of sodium amytal on these two types of movements may be interpreted as a selective effect of the drug, depressing the function relating to the orbital surface to a greater extent than those related to the convexity surface. The differences in E.E.G. readings from orbital and convexity surfaces of the brain obtained by Brazier following barbiturate administrations may also be interpreted in this manner. The clinical observation of Sargant and Slater (1954) that amytal is more effective in reducing anxiety than in reducing motor excitement could also be accounted for in terms of the differential action of the drug on different cortical areas.

Questionnaires.—The number of affirmative responses to the questionnaires was significantly increased when sodium amytal was used as a treatment and the number of doubtful responses was reduced, although not significantly. This tendency to say "Yes" more often and "?" less often under the influence of amytal was expected. It agrees with the general clinical impressions of subjects influenced by the drug; they appear to be less hesitant, cautious, and indecisive and more positive in stating their opinions.

The finding that sodium amytal failed to produce any changes on any of the questionnaire measures of neuroticism is of interest. Clinically amytal is often used for the reduction of manifest anxiety and there is no doubt that it is effective for this purpose; it would seem that sodium amytal reduces sympathetic adrenal hyperactivity. Based on a series of factor analytic studies by Wenger (1941, 1942a, 1942b, 1948), Eysenck (1954) has suggested that autonomic imbalance is the physiological concomitant of the dimension of neuroticism and that neuroticism can be described physiologically in terms of sympathetic overactivity. If this is so then one would expect that sodium amytal would significantly reduce the scores on tests which measure neuroticism. The fact that such reductions were not evident in the present study requires further confirmation. It may be that the drug has secondary effects such as drowsiness which prevent the reduction in the neuroticism scores from becoming apparent. It may also be possible that an increased tendency to reply "Yes" while under the influence of amytal obscures the expected result.

The finding that amytal apparently increases the extroversion of the subjects, as measured by Guilford's R scale, has been discussed elsewhere (Franks and Laverty, 1955). This effect may also be in part spurious in that it is related to the increased tendency to answer the questions in the "Yes" direction. (It may be that answering "Yes" more often has a greater positive influence on the R scale than on any other scale. The method of scoring used in the present study unfortunately prevents this possibility from being examined any further.) On the other hand the general unreflective nature of the drugged subject's behaviour resembles that observed in extroverted subjects and supports the hypothesis that amytal does increase extroversion. Whatever the explanation of the increase in R scores of those subjects who had received amytal it is of great interest that a drug can influence the responses to a questionnaire highly reliable under normal conditions of attitudes and opinions even when the test-retest interval is as short as five to seven days.

Verbal Question.—Pleasant mood changes, often associated with drowsiness and relief of anxiety,

were reported by subjects receiving the drug, whereas subjects who did not receive the drug reported a variety of feelings mostly indicative of some strain or discomfort. No marked or consistent changes were described by the subjects receiving placebo injections. Subjects receiving the drug consistently commented upon their relief from anxiety symptoms. It is of interest that this verbal expression of reduced anxiety did not seem to be reflected in their answers to the written questionnaires.

The subjects receiving the drug also reported less discomfort, less difficulty in sitting still, and that the air puffs were less irritating. This is in agreement with the finding that dial prevents the spread of afferent stimulation through the cortex in the receiving areas (Adrian, 1941).

The subjects given the drug tended to report that the experiment did not take a long time and that it was soon over, whereas many of the subjects who were not given the drug reported that the experiment took a long time. This is in agreement with the finding of Lindemann (1932) that normal subjects tend to underestimate time when under the influence of sodium amytal.

Summary

Sixteen introverted neurotic patients were investigated, each subject being seen twice, at an interval of about six days. Four different treatments were used, consisting of a larger dose of intravenous sodium amytal, a smaller dose, a placebo injection, and nothing. These four treatments were incorporated into the experimental design in such a way that no two subjects received the same treatment combinations. At each session the subject was given the appropriate treatment, observed for half an hour while sitting in a relaxed position in a sound-proof room, and his body movements were carefully recorded. The subject was then asked to answer certain personality questionnaires measuring introversion-extroversion and neuroticism.

The major findings were that :

(1) Sodium amytal significantly reduced the number of movements observed, in particular deep breathing.

(2) The placebo injections failed to produce any results which were significantly different from those when no injections at all were given.

(3) Sodium amytal produced no changes in the subjects' " neuroticism " scores as measured by the personality questionnaires but significantly increased their " extroversion " scores.

(4) Sodium amytal significantly increased the number of questionnaire items to which the subjects replied Yes.

(5) Sodium amytal produced reports of increased relaxation, drowsiness, relief from worry or somatic discomfort, etc.

(6) Those subjects who had received sodium amytal tended to find it easier to sit still during the experiment and tended also to underestimate the passage of time.

The implications of these findings were discussed in terms of those obtained by other experimenters in the field.

References

Adrian, E. D. (1941). *J. Physiol. (Lond.)*, **100**, 159.
Bailey, C. J., and Miller, N. E. (1952). *J. comp. physiol. Psychol.*, **45**, 205.
Brazier, M. A. B. (1954). In *Brain Mechanisms and Consciousness : A Symposium organized by the Council for International Organizations of the Medical Sciences*, p. 163. Blackwell, London.
——, and Finesinger, J. E. (1945). *Arch. Neurol. Psychiat. (Chicago)*, **53**, 51.
Cochran, W. G., and Cox, Gertrude, M. (1950). *Experimental Designs*. Wiley, New York.
Council on Pharmacy and Chemistry (1931). *J. Amer. med. Ass.*, **97**, 1886.
Eysenck, H. J. (1947). *Dimensions of Personality*. Routledge & Kegan Paul, London.
——(1952). *The Scientific Study of Personality*. Routledge & Kegan Paul, London.
——(1953). *The Structure of Human Personality*. Methuen, London.
——(1954). *Learning Theory and Personality Study*. Unpublished paper. London.
——, and Rees, W. L. (1945). *J. ment. Sci.*, **91**, 301.
Franks, C. M. (1954). *An Experimental Study of Conditioning as Related to Mental Abnormality*. Ph.D. Thesis. University of London.
——(1955). *Nature (Lond.)*, **175**, 984.
——(1956). *J. abnorm. soc. Psychol.*, **52**, 143.
——, and Laverty, S. G. (1955). *J. ment. Sci.*, **101**, 654.
Goodman, L., and Gilman, A. (1941). *The Pharmacological Basis of Therapeutics*. The Macmillan Co., New York.
Guilford, J. P. (1940). *An Inventory of Factors S T D C R*. Privately printed. Beverly Hills, Calif.
Hildebrand, H. P. (1953). *A Factorial Study of Introversion-Extraversion by means of Objective Tests*. Ph.D. Thesis. University of London.
Horsley, J. S. (1943). *Narco-analysis*. Oxford University Press, London.
Lewis, A. (1941). In *Medical Annual*, 1941, Mental Disturbance of War. Simpkin, Marshall, London.
Lindemann, E. (1932). *Amer. J. Psychiat.*, **88**, 1083.
Mallinson, W. P. (1940). *J. roy. nav. med. Serv.*, **26**, 281.
Masserman, J. H. (1938). *Arch. Neurol. Psychiat. (Chicago)*, **39**, 1250.
Mudd, S. G. (1925). *Boston med. surg. J.*, **193**, 349.
Ripley, H. S., and Wolf, S. (1947). *Psychosom. Med.*, **9**, 260.
Sargant, W., and Slater, E. (1954). *An Introduction to Physical Methods of Treatment in Psychiatry*, 3rd ed. Livingstone, Edinburgh and London.
Susselman, S., Feldman, F., and Barrera, S. E. (1946). *Arch. Neurol. Psychiat. (Chicago)*, **56**, 567.
Thorner, M. W. (1935). *J. nerv. ment. Dis.*, **81**, 161.
Trethewie, E. R. (1953). *Med. J. Aust.*, **1**, 100.
Wenger, M. A. (1941). *Psychosom. Med.*, **3**, 427.
——(1942a). *Ibid.*, **4**, 94.
——(1942b). *Hum. Biol.*, **14**, 69.
——(1948). *Comp. Psychol. Monogr.*, **19**, No. 4.
Wikler, A. (1953). *Res. Publ. Ass. nerv. ment. Dis.*, **32**, 269.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 144.

DISSEMINATED SCLEROSIS TREATED WITH ISONIAZID WITH A METHOD OF EVALUATING CHRONIC NEUROLOGICAL DISORDERS

BY

BARBARA M. ANSELL and EDWIN CLARKE

From the Postgraduate Medical School of London and Hammersmith Hospital

Recently a new therapeutic agent has been added to the list of substances that have been suggested for the treatment of disseminated sclerosis. Kurtzke and Berlin (1954) have reported encouraging results from the use of isoniazid and, in view of this, the evaluation of its effect on a small number of patients was thought desirable.

Material

Eleven patients suffering from undoubted disseminated sclerosis were studied. They had all been seen on account of a recent relapse, or, in one case, because of steady deterioration; patients manifesting the initial features of the disease were not included. Five were men and six were women with ages ranging from 27 to 48 years (mean 38 years). The disease had been present for periods of two to 21 years with a mean duration of 10. However, in only one case had it been progressive from the onset, the remainder having experienced several relapses before permanent disability appeared; the mean duration of the latter was five years. In all but one an aggravation of the existing deficits or the appearance of new features had occurred within the last two years—the average for this being nine and a third months.

Methods

In any long-standing disease, regular attendance at hospital, new treatments, and the enthusiasm of the medical attendant tend to encourage the patient and thus false assumptions may be made. From the patient's point of view, his ability to perform everyday tasks such as walking, dressing, eating, and writing are of paramount importance. Therefore, in order to reduce subjective error both on the part of the patient and the examiner the functional state of each patient was recorded on a special form (Fig. 1) at regular intervals. The assessment was made on the basis of self-care, ambulation, and function tests, in the first two the ability to perform tasks being indicated by "yes" or "no". Improvement was judged by an absolute increase in the number of positive responses and deterioration by an increase in the negative ones. These changes were amplified whenever possible by tests aimed at assessing normal function. They consisted of the strength of the grip, the time taken to walk a given distance, and the time taken to climb a set number of stairs. The distance and other circumstances, such as support, were suited to the individual patient. Standards were established from the average of repeated performances by healthy individuals. Note was also taken of change in the patient's mental state, speech, sphincter control, and physical signs. It was then possible to assemble patients into groups according to their functional abilities:

Group I.—Able to lead a normal life.

Group II.—Minimal incapacity; able to lead a normal life but aware of disabilities.

Group III.—Can walk, with or without support, but has considerable limitation of activities; can do light work or household duties.

Group IV.—Confined to a wheel chair for all practical purposes.

Group V.—Completely helpless.

Of our 11 patients, initially five were in Group III, five in Group IV, and one in Group II. The majority were investigated in hospital to establish the diagnosis beyond doubt, and an initial assessment for the purposes of this trial was made before discharge. Otherwise it was carried out at the first out-patient attendance. They were all placed on regular out-patient physiotherapy which was maintained throughout the trial, and monthly assessments were made as described above. One month after starting physiotherapy isoniazid was introduced at a standard dosage of 100 g. t.d.s. and this has been continued for periods of two and a half weeks to

Date		
SELF-CARE 1. Change position in bed		
2. Move from lying to sitting	Aided	
	Alone	
3. Move from sitting to standing	Aided	
	Alone	
4. Move from bed to chair	Aided	
	Alone	
5. Dress	Partly	
	Completely	
6. Feed self	Partly	
	Completely	
7. Write name and address		
8. Use toilet without assistance		
9. Bath without assistance		
AMBULATION 1. Able to walk with 2 sticks or instructors		
2. Able to walk with 1 stick or instructor		
3. Able to walk alone		
4. Able to walk 500 yd.		
5. Able to climb stairs holding on to railing		
6. Able to climb stairs alone		
MENTAL STATE	Abnormal	
	Normal	
SPHINCTER CONTROL	Abnormal	
	Normal	
OTHER		
FUNCTION TESTS Walking time (distance—manner)		
Climbing time (number of steps—manner)		
Grips	Right	
	Left	
Functional status (1–5)		
Change in physical signs (+,−,u)		
Overall change (+,−,u)		

FIG. 1.—Chart used for serial evaluation of functions : + = improvement, − = deterioration, u = unchanged.

eight months. Three subjects discontinued the drug at their own request two and a half, nine, and 16 weeks from beginning therapy. Six patients have received therapy for six months or more and the other two for five and one month respectively. The first assessment was designated − 1, that immediately before therapy 0, and subsequently the number indicated the month from the start of isoniazid therapy (Fig. 2). During the initial period of physiotherapy the function tests were performed at each attendance in order that the patient could get used to them and avoid apparent improvement due to familiarization with the tests. No other therapy was given at any time in this investigation and placebos were not employed.

Results

These are summarized in the Table, where cases are grouped according to the period over which the drug was administered; individual exacerbations are not shown.

TABLE
RESULTS IN 11 CASES OF DISSEMINATED SCLEROSIS TREATED WITH ISONIAZID

Month of Trial	Results			Total No. of cases.
	Better	No change	Worse	
1	0	7	4	11
2	0	8*	2	10
4	2†	5	1	8
6	1	6‡	1	8
8	1	—	1	2

Patient terminated therapy at own request, * at 2½ weeks, † at 9 weeks, and ‡ at 16 weeks (see Case 1).

After treatment had begun, a total of seven patients showed an exacerbation of their pre-existing state and in two it occurred twice with intervals of seven and five weeks respectively. In three it occurred in the first month, in two in the second, and in two in the third month of treatment. In five an aggravation of a previous defect such as ataxia, paraesthesiae, or blurring of vision took place, but in the other two new symptoms and signs appeared while the drug was being given. Of the five that deteriorated, the following case is typical.

Case 1.—In a woman aged 40, disseminated sclerosis had begun 21 years previously with transient blurring of vision, followed by temporary diplopia and retention of urine seven and 11 years later respectively. The first permanent disability had developed six years previously and consisted of leg weakness and ataxia, which fluctuated in severity. Ten weeks before isoniazid therapy was begun there was a sudden aggravation of these disabilities. Shortly after beginning therapy the symptoms increased further but then improved, only to recur with increased severity in the third month of treatment. This deterioration was adequately reflected in the function tests. Treatment was continued for a further month but as there was no improvement and a state of depression had supervened, the patient refused to cooperate further. In the next three months, with the aid of continued physiotherapy, she gradually returned to her pre-treatment level (Fig. 2).

The improvement in two patients was an increase of limb power and a decrease of ataxia. That this change might have been due to the natural course of the disease is shown by the following case :—

Case 2.—In a man aged 35 years the onset of disseminated sclerosis had been 10 years previously and was characterized by transient numbness of the legs. There were two further relapses but for five years before treatment he had noted residual disabilities in the legs and arms. Six weeks before treatment began, weakness and ataxia of the left limbs increased markedly. The physical signs were appropriate. After 11 weeks of therapy he started to improve and in six weeks returned to the state preceding the exacerbation. This state was maintained for a further three months while he was still receiving isoniazid. Limb power has increased and ataxia is less, these changes being reflected in the function tests.

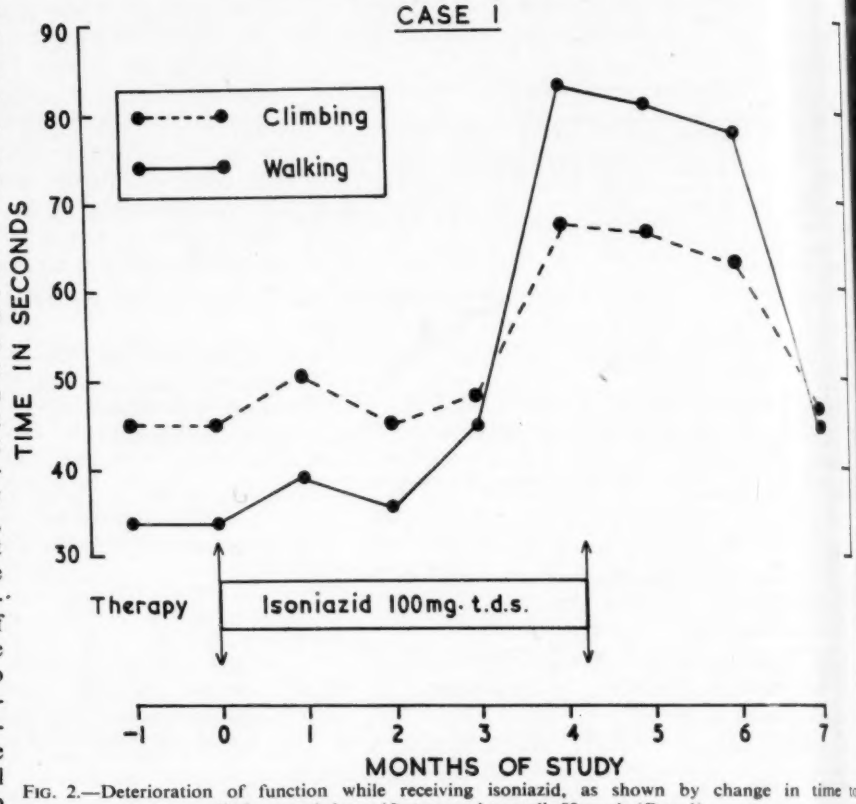


FIG. 2.—Deterioration of function while receiving isoniazid, as shown by change in time to climb up and down 10 steps and to walk 50 yards (Case 1).

In the other case improvement on the pre-treatment state was noted seven weeks after therapy had been discontinued at her own request, because of a marked exacerbation. Its relationship to the administration of the drug is thus in doubt.

Toxic Effects

Two patients suffered distressing gastro-intestinal symptoms due to their relatively small body mass (Pleasure, 1954). A third had a major epileptic seizure on the ninth day of treatment but although isoniazid was continued for a further five months he has had no more fits.

Discussion

Our findings differ considerably from those of Kurtzke and Berlin (1954) who, on the basis of an accidental observation, advocated the use of isoniazid in disseminated sclerosis. Whereas we found it of little or no value, they report excellent results, inasmuch as 90% of their patients were improved by the drug. However, the series were not strictly comparable for our patients were older, the disease was more chronic, and women were included. Otherwise, like theirs, all our patients had shown evidence of activity within the two years preceding treatment. Only two of our patients showed any improvement and in each it was not dramatic and may have represented a spontaneous fluctuation in the course of the disease. The others were either unchanged or worse. There was no indication that deterioration was but a prelude to more favourable results as Brickner (1932) observed when using quinine. One patient developed symptoms and signs of a fresh lesion while having the drug and others have also observed this (Campbell, 1955). If isoniazid is of any value in disseminated sclerosis it would have been expected to prevent relapses and produce at least some unequivocal evidence of improvement. As neither of these events has been forthcoming in a small but carefully studied series of cases there seems to be no justification for raising unnecessarily the hopes of patients with disseminated sclerosis of the type that we have investigated. The uniform failure of this medication did not induce us either to extend our series, introduce placebos, or construct a control group from previous records. We have no information, however, concerning the treatment of patients with the initial features of the disease, and relapse

rates have not been obtainable. Evaluation of these would be more difficult and demand a survey such as that proposed by Compston (1953), as well as an observation period of at least five years (MacLean and Berkson, 1951). Studies of this nature are being carried out elsewhere (McAlpine, 1955).

The criteria suggested by McAlpine, Compston, and Lumsden (1955) to evaluate the results of treatment in disseminated sclerosis are (1) the effect on acute symptoms, (2) the prevention of relapses, and (3) the effect on disability. Two of our patients had a relapse involving acute and new features but in neither were they affected by isoniazid ; in five, exacerbations were not prevented and the degree of disability, admittedly severe in all, was increased more often than decreased. By this assessment, therefore, our results were extremely disappointing.

There is no experimental evidence to suggest that isoniazid should be of any value in favourably affecting the pathological process in disseminated sclerosis. In our cases there was no reason to suppose that the drug was having any influence for it was unable to prevent exacerbations and relapses. As at times it seemed to aggravate the patient's condition, its effect was perhaps deleterious. Isoniazid may at times have toxic influences upon the nervous system (Pleasure, 1954), and, although the peripheral neuropathy that is a well recognized complication (Gammon, Burge, and King, 1953) was not observed in the present cases, one patient had a major convulsion (Reilly, Killam, Jenney, Marshall, Tausig, Apter, and Pfeiffer, 1953). The features of optic neuritis in one patient were probably due to the disease process itself rather than a toxic effect of the drug that is known to occur (Keeping and Searle, 1955).

The quantitative evaluation of the patients was an important aspect of the study. Kurtzke and Berlin (1954) and Kurtzke (1955) when assessing their cases used a scheme which was a mixture of functional state, symptoms, and signs. They thus devised 10 groups some of which would appear to be superfluous. The rehabilitation programme of Zarling (1954), which included activity rating scores, and the method used by Alexander (1951) are available for the minute consideration of patients but are too detailed for everyday use. Our method is simpler and based only upon the functional state of the patient. It has proved to be entirely adequate in the cases comprising this report, and can be readily applied to other forms of chronic neurological disease.

When the response of a neurological condition to a new therapeutic agent is being considered, objective evaluation must be used and, if possible, a quantitative method of assessing progress employed.

Summary

Eleven patients suffering from chronic disseminated sclerosis were given isoniazid for periods ranging from two and a half weeks to eight months, while assessment of their functional state was made at regular intervals.

In no case did unequivocal improvement occur ; seven patients showed an exacerbation of their previous symptomatology and two experienced a relapse with new features while receiving the drug.

It is concluded that in the moderately advanced cases considered here, isoniazid is of no therapeutic value.

A simple quantitative method of assessing changes in chronic neurological disorders is suggested.

Addendum

Since the completion of this paper further reports on the ineffectiveness of isoniazid in the treatment of disseminated sclerosis have appeared (Dekaban, 1955 ; Korengold, Haase, Berg, and Magee, 1955 ; Lønnum, 1955 ; Hinterbuchner, Goldner, Rogoff, and Rabiner, 1956). On the other hand, Tschabitscher, Wanko, Schinko, and Fust (1955) thought it was beneficial in their patients (see also Georgi and Jordan, 1956) and Schinko, Tschabitscher, and Wanko, (1955), together with Ahringsmann (1955), have resurrected the theories concerning the tuberculous origin of disseminated sclerosis and have actually identified mycobacteria in the cerebrospinal fluid of patients with this disease.

References

Ahringsmann, H. (1955). *Schweiz. med. Wschr.*, **85**, 884.
Alexander, L. (1951). *A.M.A. Arch. Neurol. Psychiat.*, **66**, 253.
Brickner, R. M. (1932). *Ibid.*, **28**, 125.
Campbell, A. M. G. (1955). Personal communication.
Compston, N. D. (1953). *Lancet*, **2**, 271.
Dekaban, A. (1955). *Canad. med. Ass. J.*, **73**, 478.
Gammon, G. D., Burge, F. W., and King, G. (1953). *A.M.A. Arch. Neurol. Psychiat.*, **70**, 64.
Georgi, F., and Jordan, D. (1956). *Schweiz. med. Wschr.*, **86**, 321.
Hinterbuchner, L. P., Goldner, M. G., Rogoff, J. B., and Rabiner, A. M. (1956). *A.M.A. Arch. Neurol. Psychiat.*, **75**, 115.
Keeping, J. A., and Searle, C. W. A. (1955). *Lancet*, **2**, 278.
Korengold, M. C., Haase, G. R., Berg, L. R., and Magee, K. R. (1955). *Neurology*, **5**, 801.
Kurtzke, J. F. (1955). *Ibid.*, **5**, 580.
——, and Berlin, L. (1954). *Amer. Rev. Tuberc.*, **70**, 577.
Lønnum, A. (1955). *Nord. Med.*, **54**, 1319.
McAlpine, D. (1955). Letter. *Brit. med. J.*, **1**, 1392.
——, Compston, N. D., and Lumsden, C. E. (1955). *Multiple Sclerosis*. Livingstone, Edinburgh.
MacLean, A. R., and Berkson, J. (1951). *J. Amer. med. Ass.*, **146**, 1367.
Pleasure, H. (1954). *A.M.A. Arch. Neurol. Psychiat.*, **72**, 313.
Reilly, R. H., Killam, K. F., Jenney, E. H., Marshall, W. H., Tausig, T., Apter, N. S., and Pfeiffer, C. C. (1953). *J. Amer. med. Ass.*, **152**, 1317.
Schinko, H., Tschabitscher, H., and Wanko, T. (1955). *Wien. med. Wschr.*, **105**, 717.
Tschabitscher, H., Wanko, T., Schinko, H., and Fust, B. (1955). *Schweiz. med. Wschr.*, **85**, 556.
Zarling, V. R. (1954). *Neurology*, **4**, 147.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 148.

ISCHAEMIC AND POST-ISCHAEMIC PARAESTHESIAE

NORMAL RESPONSES IN THE UPPER LIMB WITH SPECIAL REFERENCE TO THE EFFECT OF AGE

BY

E. W. POOLE

From the Department of Neurology, United Oxford Hospitals

Paraesthesiae consequent on peripheral nerve compression or general limb ischaemia have long attracted interest, and many features suggest their possible value in the study of peripheral nerve disorders. However, it is not certain if they are an essential feature of normal nervous function or if any significance can be attached to their absence. To clarify this and to determine features suitable as criteria of normality in the clinical application of paraesthesiae tests, the responses produced by a standard test have been studied in normal subjects of different ages. This showed that age appeared to modify the response, and the results are reported here.

The usual method of eliciting paraesthesiae is by occlusion of the circulation with a sphygmomanometer cuff applied above the elbow. During such a procedure ischaemic paraesthesiae (I.P.) appear within a minute or so as faint tingling, buzzing, or vibrating sensations in the hand spreading a variable distance up the limb before dying away some minutes later (Kugelberg, 1944; Weddell and Sinclair, 1947). On releasing the cuff post-ischaemic paraesthesiae (P.I.P.) follow (Lewis, Pickering, and Rothschild, 1931; Zotterman, 1933; Kugelberg, 1944; Weddell and Sinclair, 1947). Four elements have been distinguished (Merrington and Nathan, 1949)—thermal, pseudo-cramp, tingling, and pricking—but the present study concerns only the last two to which the term P.I.P. is here restricted. These form the prominent pins-and-needles sensation which appears distally in the hand approximately one minute after circulatory release and persists for some minutes. The presence, intensity, and duration of P.I.P. are determined by the length of provocative occlusion at any site; upper arm occlusions of seven minutes (or even less) have been found usually adequate to produce P.I.P. in previous studies. Post-ischaemic paraesthesiae, unlike I.P., require a standard period of ischaemia for any comparative assessments, and it seemed of importance in the present study to employ an occlusion normally adequate but sufficiently short to be generally tolerable (even in pathological states) and with the minimum of risk of ischaemic damage. An important associated feature of post-ischaemic responses also considered in this study is post-ischaemic muscle twitching (Reid, 1931). This occurs predominantly in the small muscles of the hand where it provides objective evidence of responses analogous to P.I.P. though less readily induced (Kugelberg, 1944, 1946, 1948; Magladery, McDougal, and Stoll, 1950; Kugelberg and Cobb, 1951).

Material and Methods

Subjects.—Two series of subjects were examined.

Series I.—This series comprised 93 normal subjects examined by a standard procedure with occlusion for 10 minutes, as described below. These were either healthy volunteers or convalescent patients free from any possible relevant defect. For inclusion they had to be (1) average or better witnesses; (2) normotensive (casual systolic pressure not exceeding 180 mm. Hg); (3) not anaemic clinically (haemoglobin level not less than 75%); and (4) with warm limbs, the interdigital cleft temperature being not less than 80° F. The ages ranged from 12 to 84 years, with average 44·6, and they were considered in four groups thus:

Group A (age 12 to 30 years)—24 subjects with average age 22·2 years.
Group B (age 31 to 45 years)—25 subjects with average age 38·2 years
Group C (age 46 to 60 years)—25 subjects with average age 53·1 years.
Group D (age 61 to 84 years)—19 subjects with average age 70·1 years.

The sex ratio was 4 : 1 in favour of males.

Series II.—This series comprised an approximately equal number of subjects, free from sensory abnormality but excluded from Series I on the following grounds: (*a*) the presence of anaemia, hypertension, or cold limbs as detailed above; (*b*) a test not of the standard 10-minute type, or not assessed in full detail; and (*c*) the

presence of non-sensory abnormalities from manifest nervous disease. The broad details of the responses in this heterogeneous series of normals and "probable" normals provided additional evidence of general trends and allowed some assessment of the influence of various factors such as anaemia.

Standard Paraesthesiae Test.—A standard period of ischaemia was arbitrarily fixed as 10 minutes of complete circulatory arrest from an above-elbow compression. This allowed adequate time for the elicitation of I.P., and was longer than that usually needed for the production of P.I.P.; and though pricking and tingling might not both occur (Merrington and Nathan, 1949), this was not considered important. Such an occlusion was usually readily tolerated, but was nevertheless near the upper limit of endurance in some instances, and was certainly often the greatest to be achieved in relevant pathological states, e.g., polyneuritis. It was adequate to assess any premature ischaemic sensory impairment, and its duration was reassuringly short from the viewpoint of vascular damage in the elderly. Though the lower limb seemed, through its greater susceptibility to both ageing and disease processes, to be a more useful field for study, the discomfort caused by such occlusions and the possibility of vascular damage were effective deterrents.

Examination.—The subjects were examined under warm and quiet circumstances. Sensory or motor symptoms past or present were carefully enquired for as well as the state of general health. The usual clinical assessments of motor, reflex, and sensory functions were augmented by the use of graded nylon hairs to test tactile perception in many instances, and by the use of a tuning fork activated to standard degrees to provide an index of vibration perception. Details as to the blood pressure, the degree of peripheral vascular sclerosis, and the existence of anaemia were noted, and as an index of limb temperature the interdigital cleft temperature was recorded with a Marks skin thermometer.

Limb ischaemia was induced by a sphygmomanometer with a bag of 23 cm. by 12·5 cm. centred over the medial aspect of the limb, its lower border being 3 to 5 cm. above the medial epicondyle. The arm was elevated for approximately 15 to 20 sec.; the cuff was then rapidly inflated to pressures of 180 to 200 mm. Hg; and finally the arm was lowered to rest lightly on a padded table, or by the side if the subject was in bed. The moment of occlusion, its duration, and the onset of sensations were noted on a stop-watch. At the end of the occlusion, the bag was disconnected and removed, the pressure falling at once to zero. In the unusual event of compression causing considerable discomfort, the occluding pressures were reduced to 150 mm. Hg where possible; in the elderly and hypertensives the pressures were increased to 220 to 230 mm. Hg, or at least 30 mm. above the systolic pressure. The level of the cuff above the medial epicondyle and the limb calibre at the mid-point of compression were later measured from the zone of hyperaemia. No strict temperature control was employed, but cooling was minimized by examining in a warm room, and in some instances having a source of radiant heat nearby.

Before occlusion the nature of the test was explained to the subject and he was instructed to concentrate on his arm and to report promptly any "feelings" which might arise, even if their precise nature was uncertain. As soon as any sensations were reported their character, distribution, site of onset, preferential reference, and proximal spread were pursued, and attention focused on the time when they had ceased or were not certainly present. If no sensations were reported, general inquiries were made as to the state of the arm every one to two minutes, and if nothing was noted by the latter part of the occlusion, specific questions were asked as to the presence at any stage of feelings of vibrating, buzzing, tingling, burning, or cold, to ensure that nothing was overlooked.

On circulatory release a similar procedure was followed. Questions as to the state of the limb were put approximately every half-minute and, when no pins-and-needles was reported after one and a half to two minutes, peripheral stimuli of squeezing and tapping of the fingers known to aggravate P.I.P. (Lewis and others, 1931; Weddell and Sinclair, 1947) were used to ascertain if any impressions could be evoked. Finally, if no sensations were reported after three minutes, the presence of pins-and-needles, buzzing, thrusting, or throbbing at any stage was directly sought to ensure that the subject was not neglecting to report them. The influence of the above peripheral stimulation on P.I.P. was noted from time to time and used to ensure that impressions could not be re-induced after their reported cessation. Later the test was discussed in retrospect and comparisons made between the ischaemic and post-ischaemic experiences. If any important feature of the responses was in doubt the test was repeated on the opposite limb and/or on the same limb after an interval of at least 24 hours. In many cases observations were made on the degree of unprovoked post-ischaemic muscle twitching visible in the first dorsal interosseous muscle.

Assessment of Responses.—Though the initial aim was merely to record the presence or absence of some form of tingling or pins-and-needles with the standard test, it became apparent that more detailed assessments of the precise time-course of the responses might be of value. Previous workers have used both the time of onset and the duration as indices of the severity of the responses with P.I.P. (and to some extent with I.P.), more intense reactions being associated with more rapid onset and longer duration. The onset of P.I.P. was abrupt and I.P. moderately so with appreciable sensations, but their cessation was more insidious especially for I.P. Where doubts arose, the end-point was taken as the mean between certain presence and absence, but no weight was placed on minor changes in I.P., and for the more definite P.I.P. the end-point was usually relatively clear, no appreciable alteration being produced by this refinement. For general analysis the times were listed to the nearest 0·1 minute.

In addition to the time-course of the responses some

crude assessment of their maximum intensity was attempted on a " + " system of grading. For I.P. this was :

+ (slight) = faint impressions of " something going on "
++ (moderate) = undoubted tingling, buzzing, or vibrating
+++ (severe) = the same, but stronger
++++ (very severe) = severe enough to cause discomfort

For P.I.P. the grading was thus :

+ (slight) = only mild tingling, even with peripheral stimulation
++ (moderate) = " real pins-and-needles ", prominent sharp sensations
+++ (severe) = pins-and-needles producing other reactions such as grimaces or whistling, especially on aggravation by peripheral stimulation
++++ (very severe) = pins-and-needles causing frank distress without peripheral stimulation

A distinction was made between I.P. and vague impressions which appeared to be purely thermal, though if the latter were prominent in the early stages of occlusion and especially if localized to any area of the hand, they were classed as "doubtful" provided all intermittent vibrating, tingling qualities were denied. In the post-ischaemic phase a distinction between pricking and tingling was attempted only in so far as estimating whether any sharp pricking pins-and-needles was present at any time.

Assessments of induced muscle twitching were based on the maximum visible unprovoked activity at any stage in the small muscles of the hand, crudely graded thus :

+ (slight) = just visible
++ (moderate) = obvious but not moving the finger
+++ (severe) = considerable with evident finger movements
++++ (very severe) = striking with gross finger movements

Results

Series I.—These results were found in normal subjects.

Ischaemic Paraesthesiae.—The analysis of the results for I.P. appears in the Table at (a). The incidence of occurrence has been given in three classes, " definite ", " doubtful ", and " absent " ; " doubtful " indicates vague or inconstant impressions, possibly purely thermal. In the youngest group (A) definite responses were always obtained, but in the oldest group (D) these occurred in little more than one-third of the subjects. This decreasing trend of response with age was also shown in the plus intensity grading, and further, where distinct impressions were present in the older groups, the mean onset was slightly delayed, a change to be expected with less intense responses (Kugelberg, 1944, 1948). Though the mean duration of the definite I.P.

TABLE

ISCHAEMIC AND POST-ISCHAEMIC PARAESTHESIAE IN 93 NORMAL SUBJECTS WITH 10-MINUTE OCCLUSION TESTS (SERIES I)

Age Group	A (12–30 yr.)	B (31–45 yr.)	C (46–60 yr.)	D (61–84 yr.)
No. of Subjects	24	25	25	19
(a) *Ischaemic Paraesthesiae*				
Incidence of I.P.				
Definite	24 (100%)	18 (72%)	18 (72%)	7 (37%)
Doubtful	0 (0%)	1 (4%)	4 (16%)	1 (5%)
Absent	0 (0%)	6 (24%)	3 (12%)	11 (58%)
Mean intensity (+ grading)				
All subjects	1·9	1·4	1·1	0·5
" Definites "	1·9	1·8	1·6	1·1
Onset (min.) after occlusion in those with definite I.P.				
Mean and (S.D.)	1·4 (0·42)	1·5 (0·58)	2·1 (1·00)	1·8 (0·56)
Limits	0·8–2·5	0·5–2·8	0·8–3·5	1·0–2·5
Duration (min.) of definite I.P. (to limit of occlusion)				
Mean and (S.D.)	6·1 (1·66)	6·4 (2·05)	5·5 (1·55)	6·0 (2·90)
Limits	2·5–9·2	3·0–9·5	3·5–8·7	2·5–9·0
Nos. with I.P. to or above mid-forearm	4	4	2	0
(b) *Post-ischaemic Paraesthesiae*				
Incidence of P.I.P.				
Definite	24 (100%)	25 (100%)	25 (100%)	15 (79%)
Absent	0 (0%)	0 (0%)	0 (0%)	4 (21%)
Nature : No. with undoubted sharp pricking	24 (100%)	25 (100%)	21 (84%)	7 (37%)
Mean intensity (+ grading)	2·4	2·2	2·1	1·1 (all cases) 1·4 (with P.I.P.)
% Lacking accentuation by " tapping "	4% (24 assessed)	29% (17 assessed)	53% (19 assessed)	62% (13 assessed)
Onset (min.) after circulatory release in subjects with P.I.P.				
Mean and (S.D.)	1·0 (0·24)	1·0 (0·26)	1·1 (0·35)	1·4 (0·34)
Limits	0·6–1·5	0·6–1·5	0·7–2·5	0·9–2·7
Duration (min.)				
Mean and (S.D.)	5·3 (1·80)	4·6 (1·14)	4·2 (1·37)	2·6 (1·64) (all cases) 3·3 (1·11) (with P.I.P.)
Limits	3·5–11·7	2·3–6·5	2·2–7·1	0–5·5
No. with P.I.P. confined to fingers	2 (8%)	3 (12%)	4 (18%)	6 (32%)
Post-ischaemic muscle twitching				
Present	73% 36% (22 assessed)	75% 8% (12 assessed)	67% 7% (15 assessed)	50% 7% (14 assessed)
Severe				

showed some reduction in the older groups (bearing in mind the small number of " definites " in group D), little weight can be put on this slight change in view of the difficulty in determining precise end-points with I.P. In the younger groups paraesthesiae more often extended to or above the mid-forearm level, a spread in keeping with their greater intensity (Kugelberg, 1944). In all groups I.P. were often preferentially referred to ulnar but not median nerve territory, as previously described (Weddell and Sinclair, 1947 ; Gilliatt and Wilson, 1953). There was no evidence for any sex difference in the incidence of occurrence of I.P. when the small female group was considered separately.

Post-ischaemic Paraesthesiae.—The analysis of P.I.P. results appears in the Table at (b). In contrast to I.P., P.I.P. occurred with remarkable constancy, distinct sensations being reported by all subjects except four in the oldest group (D). However, sharp pricking sensations were, as far as could be judged, frequently absent in the older groups, and peripheral stimuli often failed to accentuate the impressions. Moreover, the average intensity based on the plus grading showed a steady decline, all suggesting a diffuse reduction in the response with advancing years. Further, this was clearly evident in the mean onsets and durations, the former increasing and the latter decreasing in the older groups, both in keeping with decreasing intensities of response (Lewis and others, 1931 ; Zotterman, 1933 ; Weddell and Sinclair, 1947). The equation of regression of duration of P.I.P. with age was

$$y = 6{\cdot}43 - 0{\cdot}049\,x$$

where y = duration of P.I.P. in minutes and x = age in years. The regression was highly significant (standard error of regression coefficient = 0·009 $P<0{\cdot}1\%$). The mean onset in group D was significantly above that in other groups combined ($P<0{\cdot}1\%$). Further evidence on the same theme was provided by the rising incidence of subjects with sensations which were confined to the fingers, a feature of less intense responses (Lewis and others, 1931 ; Zotterman, 1933 ; Weddell and Sinclair, 1947). Pricking-tingling distinctions were not stressed because of the difficulty of establishing differences independent of intensities, but these results favoured a general reduction rather than a selective impairment of either of these elements.

In sharp contrast to I.P., P.I.P. were usually diffusely referred to the hand, and though they might be first noticed patchily in median or ulnar nerve territories, the complete selective involvement of one territory was not seen. However, some preferential reference to areas on the radial or ulnar side of the hand was seen in 12 instances, 10 favouring the former and two the latter. The radial preference was noted in the younger groups.

Post-ischaemic Muscle Twitching.—Though observations were not made in all subjects and the assessments were crude, the incidence of distinct twitching was lower than for I.P. or P.I.P. (Table (b)). This finding was in keeping with the fact that sensory responses are more readily induced than motor (Kugelberg, 1944, 1946, 1948). Such twitching predominated in the young, where it appeared more severe (Table (b)).

Series II.—In this group of normal and near-normal subjects the incidence of occurrence of I.P. and " 10-minute " P.I.P. showed the same decrease in response with age. In the usual four age groups A, B, C, and D, I.P. were clearly present in 93%, 77%, 59%, and 29% respectively (total subjects = 96). Post-ischaemic paraesthesiae were elicited in 65 subjects (10 in group D) with occlusions of 10 minutes or less, and were lacking in six subjects (four in group D) with occlusions of 10 minutes or longer. However, in four subjects (two in group D) the P.I.P. were only transient after 10-minute occlusions, so that, as with I.P., the proportion of subjects with little or no response was greater than in Series I. This appeared to be partly due to dull witnesses in Series II (which was unselected in this respect), but there were other noteworthy features. Thus subjects with severe wasting from motor neurone disease formed the only two entirely lacking P.I.P. outside the oldest group (D), and the only good witness lacking clear I.P. in the youngest group (A) ; so that if these and poor witnesses were excluded, definite I.P. were invariably present in the young, and " 10-minute " P.I.P. in all but a minority of the elderly as in Series I.

The general similarity of the results in both series suggested that factors of hypertension, anaemia, and cool limbs were not of great importance. Though the numbers were small, subjects with these " abnormalities " were considered separately to see if this was confirmed. Sixteen hypertensive and 13 anaemic (haemoglobin 55 to 74%) subjects showed results closely similar to those in Series I. Moreover, paraesthesiae were elicited with incomplete circulatory arrest as previously reported (Weddell and Sinclair, 1947 ; Merrington and Nathan, 1949), so that any minor leak could scarcely account for major defects. However, the responses in 16 subjects with cool limbs (cleft temperature $< 78°$ F.) differed from those in Series I in showing an exaggeration of ageing trends. Thus I.P. were more frequently lacking in the older groups, and P.I.P. more prolonged in the younger than might be expected from results in Series I. Nevertheless this effect was not

marked since the results in 12 subjects who had had repeated tests on the same or opposite limb when warm and cool (interdigital cleft temperature differences 7 to 18° F.) revealed no great change. Repeated water-bath experiments in an experienced young subject with thorough warming and cooling of the limbs to extremes of 97° F. and 60° F. showed a slight diminution of I.P. in the cold tests with a prolongation of P.I.P. of up to 20%. Previous workers have reported either no change (Weddell and Sinclair, 1947) or effects of this type (Bazett and McGlone, 1931 ; Lewis and others, 1931 ; Merrington and Nathan, 1949). It thus appeared advisable to avoid wide temperature differences in comparative assessments, though the usual range of clinical variation seemed unlikely to disturb essential issues.

P.I.P. in Occlusions Greater or Less than 10 Minutes.—The responses after prolonged occlusions were not studied extensively in view of the danger in the elderly. Occlusions of seven to 32 minutes' duration in 35 subjects (ages 18 to 44 years) were compared with those of seven to 27 minutes' duration in 13 older subjects (age 48 to 64 years). This confirmed that P.I.P. were usually shorter lived in the older subjects.

Constancy of Results.—The constancy of paraesthesiae responses in experienced subjects has been previously established (Lewis and others, 1931 ; Weddell and Sinclair, 1947 ; Merrington and Nathan, 1949) and is entirely supported by present studies. Analysis of the results of repeated tests in the same or opposite limb of over 50 subjects in this and allied investigations (Poole, 1954) showed that the responses were essentially symmetrical and reproducible in inexperienced subjects. The few discrepancies as to the presence or absence of I.P. occurred only when these were very faint and where there was some complicating factor such as excessive discomfort, a poor witness, or a large temperature difference. Though individual variations in the actual time course of I.P., and to a lesser extent of P.I.P., occurred, the mean group responses for the initial and repeat tests were very similar. There was evidence of a slight " practice " effect, the mean onset of P.I.P. being reduced by $<10\%$ in a repeat series, and the mean duration prolonged similarly. Thus there were no grounds for doubting the validity of the broad details of isolated performances in paraesthesiae assessments. In lower limb occlusions Marshall (1952) found experienced and inexperienced subjects achieved the same test-retest consistency. It might be noted that the only instance of a marked right-left difference occurred in a young subject with hysterical symptoms who consistently denied all paraesthesiae in one limb, but nevertheless showed prominent post-ischaemic muscle twitching bilaterally.

Relationship between Defects in I.P. and P.I.P.—There appeared to be a simple connexion between I.P. and P.I.P. in that where I.P. were present P.I.P. followed, but where I.P. were lacking P.I.P. were usually of shorter duration than the group mean and might be entirely absent. This suggested that had the standard occlusion been shorter, P.I.P. might have been lacking as frequently as I.P. This association of defects in individual cases reflected the trends seen in the series as a whole, and suggested some common factor was responsible. It was noteworthy that, apart from the hysterical patient mentioned above, muscle twitching was never unequivocally present in the absence of P.I.P., suggesting a common reduction in iterative responses. From the practical viewpoint it was apparent that if I.P. were clearly present there was no need to continue the occlusion to ascertain if P.I.P. would follow. The occurrence of post-ischaemic muscle twitching in the absence of P.I.P. might also attract attention.

Subjects Lacking I.P. and P.I.P.—There was no clear difference between subjects with and without I.P. or P.I.P., and the latter were not inferior witnesses. Two subjects, one lacking and one with minimal I.P., undergoing repeated tests, noted sensations of burning and possibly tingling at sites of recent trauma during ischaemia as Nathan (1953) reported, thus showing their acuity as observers and the fact that impressions not unlike paraesthesiae could arise in appropriate circumstances.

An obvious possible factor to be considered was the long-established ageing change in vibration perception. However, this is not agreed in the upper limbs (Pearson, 1928 ; Gray, 1932 ; Laidlaw and Hamilton, 1937 ; Cosh, 1953), though since I.P. are relatively mild sensations slight changes might be relevant. No attempt was made to assess absolute vibratory thresholds as a routine, and in group D (Series I) there was with the usual clinical testing no clear suggestion of consistently better preserved acuity in subjects with I.P. However, in other studies (Poole, 1954) involving repeated estimations of vibration perception with a Symns tuning fork (Symns, 1912, 1917) in younger subjects, the thresholds were generally slightly higher in those lacking marked I.P.

Discussion

This study shows features of paraesthesiae sufficiently uniform for use as criteria of normality

in nervous disease (and disturbed ionic states) provided age is taken into account. Thus, though exceptions may occur, the absence of I.P. in the young and of " 10-minute " P.I.P. in any except the elderly may readily attract attention. The influence of age provides a possible explanation for divergencies in previous reports as to the invariable occurrence of I.P. in upper arm occlusions (Weddell and Sinclair, 1947 ; Sinclair and Hinshaw, 1951 ; Cosh, 1953 ; Gilliatt and Wilson, 1953, 1954), and is in keeping with the occasional absence of paraesthesiae reported in the lower limb (Marshall, 1952) where ageing changes might be more marked. The lack of paraesthesiae despite any manifest sensory impairment is not surprising, since in any limb paraesthesiae are not referred uniformly to all surfaces of the hand. Factors determining this asymmetry (and the distal reference of paraesthesiae) are not established, but such results suggest that paraesthesiae assessments may provide a sensitive index of nerve function. This possibility is supported by other evidence such as the fact that after a period of limb ischaemia though sensation rapidly returns to normal (Lewis and others, 1931) paraesthesiae may not be elicited to their full extent again for many hours (Merrington and Nathan, 1949). Studies (to be reported) in polyneuritis, where distal innervation is also preferentially involved, confirm the sensitivity and possible value of such assessments as indices of affection.

The basis for the ageing changes is of importance to indicate the type of lesion when such defects occur in nervous disease, and also as a contribution to the study of ageing processes. The possibility that decreasing mental acuity was responsible must be considered, but is offset by the diffuseness and internal consistency of the changes, including also objective assessments of post-ischaemic muscle twitching. Decreased efficiency of limb compression by vascular or tissue sclerosis would not seem adequate explanation, since complete circulatory occlusion is not essential for the production of paraesthesiae. Moreover, associated observations on sensory impairment (Poole, 1954) showed that the induced sensory defects, rather than being delayed, were in some respects possibly earlier in onset in the elderly, though this might be due to the absence of I.P. allowing of uncomplicated assessment. However, fibrosis might act in a more subtle way such as by impairing ionic diffusions, e.g., K^+ from ischaemic muscle. Changes with age in blood calcium (Carlson, 1952) or *p*H (Shock, 1952; Shock and Yiengst, 1950) do not provide a satisfactory explanation. Lowered nerve temperature with age must be considered (Wagman and Lesse, 1952) but, though temperature effects may be complex, the paraesthesiae responses elicited from cool limbs and other evidence (Adrian, 1930 ; Katz, 1936 ; Hoff and Grant, 1944 ; Norris, Shock, and Wagman, 1953) do not favour this explanation.

The most likely origin for the changes would seem to lie in the peripheral nerves in three possibly interrelated fields : (*a*) reduction in fibre numbers ; (*b*) alterations in fibre relationships from connective tissue infiltration with or without fibre degeneration ; and (*c*) changes in nerve function without necessarily an obvious structural basis, such as in those properties determining the accommodation and relative repetitiousness of motor and sensory fibres (Skoglund, 1942 ; Granit and Skoglund, 1943 ; Kugelberg, 1944). In this last respect it is noteworthy that the essential feature of the ageing patterns is a change towards the motor type of response with a lesser tendency for repetitive discharges. It is not possible to discuss the many relevant ageing changes in nerve structure (Cottrell, 1940; Rexed, 1944 ; Corbin and Gardner, 1937 ; Gardner, 1940) and function (Green and Bender, 1953 ; Boman and Jalavisto, 1954 ; Petersen and Kugelberg, 1949 ; Laidlaw and Hamilton, 1937), but mention might be made of the progressive reduction in the maximum conduction velocity of ulnar nerve fibres with age (Wagman and Lesse, 1952 ; Norris and others, 1953) similar to the reduction in duration of P.I.P. This has been attributed to altered membrane properties rather than to fibre degeneration which has been considered insufficiently extensive. This raises the possibility that a change in iterative tendencies may precede functional (or structural) fibre disruption.

It is noteworthy that when a limb undergoes repeated occlusions over a short period, paraesthesiae are progressively reduced in a manner closely similar to ageing changes (Weddell and Sinclair, 1947 ; Merrington and Nathan, 1949). This might favour a chronic ischaemic aetiology and suggests some relationship with factors determining the heightened ischaemic susceptibility of motor and sensory functions after an ischaemic episode (Lewis and others, 1931 ; Barlow and Pochin, 1948) though this latter is not clearly evident in ageing. Another factor to be considered is myelin impoverishment since paraesthesiae are readily disturbed in polyneuritis. Clearly many changes may be primarily or secondarily responsible ; further studies of factors determining the nervous discharges and of ageing changes in fibre characteristics may clarify this.

Conclusions

Ischaemic and post-ischaemic paraesthesiae decrease with ageing; certain features appear sufficiently constant to provide clinical criteria of normality provided age is taken into account.

Thanks are due to Dr. W. Ritchie Russell and Dr. C. W. M. Whitty for criticism of the text, and to N. M. Bailey, M.A., for statistical advice. The work was performed during the tenure of a Henry Goodger Scholarship.

References

Adrian, E. D. (1930). *Proc. roy. Soc. B.*, **106**, 596.
Barlow, E. D., and Pochin, E. E. (1948). *Clin. Sci.*, **6**, 303.
Bazett, H. C., and McGlone, B. (1931). *Proc. Soc. exp. Biol. (N.Y.)*, **29**, 87.
Boman, K., and Jalavisto, E. (1954). *Acta physiol. scand.*, **30**, 303.
Carlson, A. J. (1952). In *Cowdry's Problems of Ageing*, 3rd ed., p. 347. Williams and Wilkins, Baltimore.
Corbin, K. B., and Gardner, E. D. (1937). *Anat. Rec.*, **68**, 63.
Cosh, J. A. (1953). *Clin. Sci.*, **12**, 131.
Cottrell, L. (1940). *Arch. Neurol. Psychiat. (Chicago)*, **43**, 1138.
Gardner, E. (1940). *Anat. Rec.*, **77**, 529.
Gilliatt, R. W., and Wilson, T. G. (1953). *Lancet*, **2**, 595.
——, ——(1954). *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 104.
Granit, R., and Skoglund, C. R. (1943). *J. Neurophysiol.*, **6**, 337.
Gray, R. C. (1932). *Minn. Med.*, **15**, 674.
Green, M. A., and Bender, M. B. (1953). *A.M.A. Arch. Neurol. Psychiat.*, **69**, 577.
Hoff, H. E., and Grant, R. S. (1944). *J. Neurophysiol.*, 7, 305.
Katz, B. (1936). *J. Physiol. (Lond.)*, **88**, 239.
Kugelberg, E. (1944). *Acta physiol. scand.*, **8**, Suppl. 24.
——(1946). *Brain*, **69**, 310.
——(1948). *Arch. Neurol. Psychiat. (Chicago)*, **60**, 140.
——, and Cobb, W. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 88.
Laidlaw, R. W., and Hamilton, M. A. (1937). *Bull. neurol. Inst. N.Y.*, **6**, 494.
Lewis, T., Pickering, G. W., and Rothschild, P. (1931). *Heart*, **16**, 1.
Magladery, J. W., McDougal, D. B. Jr., and Stoll, J. (1950). *Bull. Johns Hopk. Hosp.*, **86**, 313.
Marshall, J. (1952). *Journal of Neurology, Neurosurgery and Psychiatry*, **15**, 242.
Merrington, W. R., and Nathan, P. W. (1949). *Ibid.*, **12**, 1.
Nathan, P. W. (1953). *Ibid.*, **16**, 144.
Norris, A. H., Shock, N. W., and Wagman, I. H. (1953). *J. appl. Physiol.*, **5**, 589.
Pearson, G. H. J. (1928). *Arch. Neurol. Psychiat. (Chicago)*, **20**, 482.
Petersen, I., and Kugelberg, E. (1949). *Journal of Neurology, Neurosurgery and Psychiatry*, **12**, 124.
Poole, E. W. (1954). Unpublished observations.
Reid, C. (1931). *Quart. J. exp. Physiol.*, **21**, 243.
Rexed, B. (1944). *Acta psychiat. (Kbh.)*, Suppl. 33.
Shock, N. W. (1952). In *Cowdry's Problems of Ageing*, 3rd ed. p. 429. Williams and Wilkins, Baltimore.
——, and Yiengst, M. J. (1950). *J. Geront.*, **5**, 1.
Sinclair, D. C., and Hinshaw, J. R. (1951). *Quart. J. exp. Psychol.*, **3**, 49.
Skoglund, C. R. (1942). *Acta physiol. scand.*, **4**, Suppl. 12.
Symns, J. L. M. (1912). *Brit. med. J.*, **1**, 539.
——(1917). *Quart. J. Med.*, **11**, 33.
Wagman, I. H., and Lesse, H. (1952). *J. Neurophysiol.*, 15, 235.
Weddell, G., and Sinclair, D. C. (1947). *Journal of Neurology, Neurosurgery and Psychiatry*, **10**, 26.
Zotterman, Y. (1933). *Acta med. scand.*, **80**, 185.

THE FEBRUARY (1956) ISSUE

The February (1956) issue contains the following papers :—

Cryptic Arteriovenous and Venous Hamartomas of the Brain. J. V. Crawford and Dorothy S. Russell.

The Action of the Phosphatases of Human Brain on Lipid Phosphate Esters. K. P. Strickland, R. H. S. Thompson, and G. R. Webster.

The Effect of the Duration of Vitamin-A Deficiency in Female Rabbits upon the Incidence of Hydrocephalus in their Young. J. W. Millen and D. H. M. Woollam.

A Clinical Correlation Between Encephalopathy and Papilloedema in Addison's Disease. Antony Jefferson.

Benign Intracranial Hypertension. Peter Bradshaw.

Hyperostosis Frontalis Interna. S. Smith and R. E. Hemphill

A Family with the Progressive Hypertrophic Polyneuritis of Dejerine and Sottas. P. D. Bedford and F. E. James.

Growth of the Skull in Young Children :
Part I : Standards of Head Circumference. C. K. Westropp and C. R. Barber.
Part II : Changes in Head Shape. C. R. Barber and D. Hewitt.

Altered Response to Small Doses of Insulin Associated with Electroplexy and Hypoglycaemic Therapies. E. Marley.

The Value of the Marchi Method for Staining Tissue Stored in Formalin for Prolonged Periods. Marion C. Smith, Sabina J. Strich, and Peter Sharp.

Book Reviews

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 155.

FAMILIAL PERONEAL MUSCULAR ATROPHY AND ITS ASSOCIATION WITH THE FAMILIAL ATAXIAS AND TREMOR AND LONGEVITY

BY

RAYMOND HIERONS

From the Department of Neurology, King's College Hospital, and the National Hospital, Queen Square, London

For more than half a century descriptions of familial disorders of the nervous system showing marked differences in the clinical pattern of the malady from one member to another have been recorded. Hodge (1897) described three sibs suffering from Friedreich's ataxia, who had various combinations of muscular atrophy and loss of the posterior columns. Marie (1906) and Boveri (1911) were probably the first to emphasize that in families showing atrophy of the peroneal muscles and hypertrophy of the peripheral nerves occasional cases of familial ataxia could occur. Spiller (1910) discussed the problem in detail and reported two cases of Friedreich's disease with muscular wasting similar to that in peroneal muscular atrophy. One of these cases was studied histologically, when, in addition to the characteristic findings of Friedreich's disease, changes were also evident in the peripheral nerves. Similarly, Biemond (1928) described five families with peroneal muscular atrophy, in which isolated cases of Friedreich's ataxia occurred. In one of these families a single case of hypertrophic interstitial polyneuritis was discovered, thus suggesting a relationship between this condition and that described by Dejerine and Sottas. Greenfield (1912), van Bogaert and Moreau (1940), and Ross (1942) also described this relationship of Friedreich's disease with peroneal muscular atrophy. Spillane (1940) described a family with 21 members, 16 of whom showed signs of the so-called Roussy-Levy syndrome which includes pes cavus, absent reflexes, occasional wasting of the hypothenar muscles, kyphoscoliosis, and, rarely, dementia. Four cases had an explosive type of dysarthria; two or perhaps three showed signs of typical peroneal muscular atrophy and one showed Friedreich's ataxia. Roth (1948) describes this same association of Friedreich's ataxia with the Charcot-Marie-Tooth disease, together with a marked tendency to psychopathic behaviour in one of the families. He discusses the variability from one member to another on the basis of Haldane's (1941) hypothesis that three or four genes produce each "different" disease and that each gene is responsible for the onset at a particular age. As the result of the effect of genetic modifiers on the main gene and multiple allelomorphs further differences in the clinical pattern can occur.

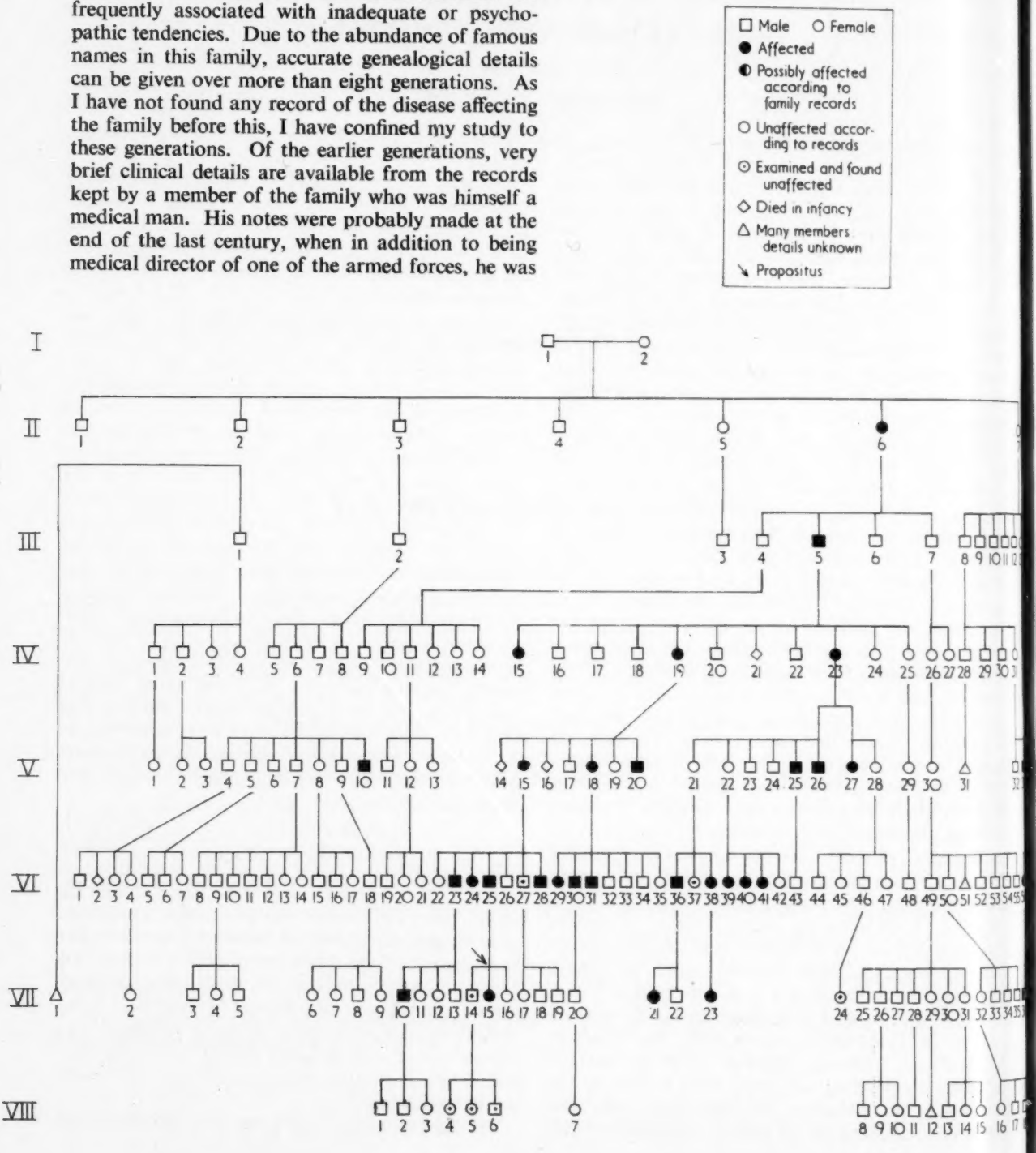
Turning now to the question of the existence, as a separate entity, of Marie's hereditary ataxia, Holmes (1907) expressed the view that "neither clinical nor pathological experience justifies its retention as the descriptive title of a form of disease", urging that it could not be distinguished from Friedreich's ataxia. Bell and Carmichael (1939), after surveying over 1,000 cases from the literature and 100 of their own, produced strong evidence for the unity of the Friedreich and Marie types. In addition they pointed out a clinical relationship between the hereditary ataxias and hereditary spastic paraplegia. Although Sjögren (1943) attempted to cast doubts on these conclusions, a recent clinical study by Schut (1950) of 22 cases of hereditary ataxia descended from a common ancestor revealed examples of these three clinical conditions. He examined five cases pathologically with Haymaker and found various combinations of the changes in Friedreich's ataxia, olivopontocerebellar atrophy, and bulbar palsy (Schut and Haymaker, 1951).

Even in such an apparently clearly defined disease as Leber's optic atrophy, Ferguson and Critchley (1928) described a family in which, in addition to typical cases, others occurred with pyramidal signs, posterior column signs, or even dysarthria. This suggested a transition between Leber's disease and Marie's ataxia. Bickerstaff (1950) described a family with 25 affected members suffering from spastic paraplegia, two having in addition retro-bulbar neuritis progressing to optic atrophy. Van Leeuwen and van Bogaert (1949) have also described this association of retro-bulbar neuritis with the hereditary ataxias.

The family which I now describe illustrates this

variation from one member to another. Its chief interest is that a large number, including quite a few affected members, achieved considerable distinction, the most famous being reformers, writers, judges, admirals, or generals. From the literature, one forms the impression that these disorders are frequently associated with inadequate or psychopathic tendencies. Due to the abundance of famous names in this family, accurate genealogical details can be given over more than eight generations. As I have not found any record of the disease affecting the family before this, I have confined my study to these generations. Of the earlier generations, very brief clinical details are available from the records kept by a member of the family who was himself a medical man. His notes were probably made at the end of the last century, when in addition to being medical director of one of the armed forces, he was a medical adviser to Queen Victoria. The diagnostic label which he gave to the malady was " hereditary muscular atrophy ".

The family tree is shown in the Figure.



The Affected Members

Case 1 (VII 15).—The propositus, a woman aged 36, was admitted to the National Hospital (No. 32096) in July, 1952, under the care of Dr. Macdonald Critchley. In infancy she suffered from meningitis during which she was unconscious for several days. This may explain why she was always considered to be less intelligent than the rest of the family and as a result was sent to a boarding school where examinations were not considered important. She has, however, been able to manage a clerical job for several years.

During childhood she was never able to walk on her toes and at the age of 18 several orthopaedic operations were carried out on her deformed feet, including division of both Achilles tendons. Her handwriting has always been shaky and her walking unsteady and both have deteriorated over the years.

After her mother's death a year before admission, symptoms of anxiety and depression developed and this was the chief reason for her coming into hospital.

Examination revealed no abnormalities of cranial nerve function except for first degree vestibular nystagmus to both sides and also on upward deviation. In the motor system there was wasting of the small muscles of the hands, the lower forearms, and also below the knees. In addition, tremor of both hands at rest and increased by movement, while rapid alternating movements were slowly and irregularly carried out, especially on the right. Reflexes were present except for the ankle jerks, and both plantar responses were extensor. Sensory testing revealed that appreciation of pain and light touch was impaired below the knees while vibration was not appreciated below the costal margins, although passive movements of fingers and toes were accurately assessed.

While in hospital, her symptoms of anxiety and depression improved and she was able to return to work, but she was readmitted in January, 1953, because of their recurrence. No appreciable change was noted in the physical signs. She was seen by Dr. C. S. Hallpike who confirmed spontaneous nystagmus without any appreciable change with the head back to either side. Cochlear function was normal and caloric responses were found to be brisk and equal. He detected an unusual alteration in optokinetic nystagmus which was abolished to the left and reduced to the right, suggestive of a high brain-stem lesion.

This case appeared to have a basis of peroneal muscular atrophy with the addition of nystagmus, static tremor increased on movement, and bilateral cerebellar signs.

This patient's younger sister (VII 16) aged 29 had no special symptoms but had high arched feet and diminished appreciation of vibration at the ankles.

Case 2 (VI 28).—This was a male, aged 73. During childhood he tended to catch his toes in walking and he recalls that while still a midshipman in the Navy he stumbled on several occasions in getting from one boat to another and as a result fell into the sea. At about the age of 35 he became rather more unsteady and describes how this forced him to give up his favourite recreation of walking in St. James's Park after his duties at the Admiralty, fearing that he might be thought to be the worse for drink. Soon afterwards a physician noticed muscular wasting of the hands. As the weakness of his feet increased he was fitted with toe springs and with these hidden under his trousers, he was able to continue in the Navy, reaching the rank of Vice-Admiral at the age of 48. His retirement at this age was not caused by his complaint. After his retirement he was ordained as a clergyman and in spite of increasing weakness of the hands continued as the vicar of a busy parish for more than 20 years until a recent fall caused a fracture of the neck of the femur.

On examination, his speech and intellectual functions were normal. Fine horizontal nystagmus on lateral deviation to either side and reduced visual acuity in the right eye from cataract were the only abnormalities of cranial nerve function found. Wasting of the small muscles of the hands, especially of the first interosseous spaces, and to a slight degree of the lower forearms, but marked in the legs with pes cavus, was found. Fasciculation was not observed. Tremor was obvious in the fingers, abolished at rest but increased on voluntary movement. Rapid alternating movements in the upper limbs were carried out irregularly. Reflexes were all obtained with difficulty; plantar responses were extensor. Sensory testing revealed slight impairment to light touch and pain below the knees, defective appreciation of passive movements at the toes, and loss of vibration sense below the costal margins. No defect to any form of sensation was found in the upper limbs. The peripheral nerves were not thickened. Because of the recent fracture, it was not possible to see him standing or walking.

The condition in this case appeared to be peroneal muscular atrophy with the addition of bilateral extensor plantar responses, nystagmus, and tremor.

Case 3 (VI 25).—This was an elder brother of Case 2 and father of Case 1, and was aged 78. He was not a very reliable witness and insisted that he was not suffering from the family trouble. He attributed his unsteadiness in walking to an amputation of the left arm disturbing the centre of gravity. Notes by his doctor father, however, contain the brief reference that his feet were affected, probably when he was about 15 years old. In spite of this he was able to enter the Navy and rose to the rank of Commander until the loss of his arm forced him to retire while still under the age of 40, when he first noticed slight weakness of the remaining hand.

Examination showed evidence of mild intellectual impairment; otherwise there was no abnormality of special senses or cranial nerve function. There was no nystagmus. The remaining hand and both legs were wasted similarly as in Case I. There was no tremor, however, nor were there signs of incoordination in the right arm, but in the lower limbs there was marked ataxia probably due to impairment of postural sense. Reflexes were normal except for the ankle jerks which were absent.

Although the patient was unreliable as a sensory witness it seemed that appreciation of passive movements

was impaired at the toes and vibration sense lost below the iliac crests.

There was a slight degree of scoliosis in the upper dorsal spine.

He had marked Rombergism and, when walking, bilateral foot drop and a high-stepping type of gait.

This seemed to be a typical case of peroneal muscular atrophy.

Case 4 (VI 38).—This woman, aged 77, was the wife of a general. Until about the age of 40 she claims that she was normal in every way. At this time she first found difficulty in walking which was followed by weakness of the hands. These symptoms have gradually increased and in recent years tremor of the hands has developed.

Examination showed wasting of the small muscles of the hands and also below the knees. A static tremor of the hands very like that of Parkinsonism was present but was much accentuated by movement. Below the knees, sensibility to pain and light touch were impaired together with postural loss at the toes.

This patient appeared to be suffering from peroneal muscular atrophy with the addition of tremor.

Case 5 (VII 23).—This woman, aged 39, was the only daughter of Case 4. About 10 years earlier, while serving as a V.A.D. in an ophthalmic department, she first noticed tremor of the hands. In recent years she has found increasing difficulty in walking.

Physical signs included tremor of the outstretched hands, not increased by movement, clawing of the toes and severe weakness of dorsiflexion of both feet. Unlike the previous cases, no wasting or weakness was observed in the upper limbs. The only sensory impairment was loss of vibration sense below the iliac crests.

This case could perhaps be classified as peroneal muscular atrophy confined to the lower limbs with the addition of tremor of the hands.

Case 6 (VII 21).—This patient, aged 36, was the daughter of a High Court judge who was himself afflicted with the malady from adolescence until his death at the age of 66.

She began to have difficulty in walking at about the age of 8 and noticed weakness of the hands a few years later.

Examination revealed marked wasting of the small muscles of the hands and marked wasting below the knees. The knee and ankle jerks were absent and no response was obtained from plantar stimulation but the power of dorsiflexion of the feet and toes was lost. Postural loss at the toes appeared to be the only sensory defect.

This appeared to be a typical case of peroneal muscular atrophy.

The following three cases are sisters who were also examined, though unfortunately not under ideal circumstances.

Case 7 (VI 39).—A woman, aged 72, has been unsteady in walking since childhood and, at the age of 30, operations were performed on both feet. Since then the hands and feet have slowly become weaker and for 20 years she has been obliged to wear walking irons. An arthrodesis of the left ankle was performed a few years ago which improved her walking considerably.

Abnormal physical signs included first degree vestibular nystagmus to either side, and some wasting below the knees, wasting of the hands with clawing of the fingers which was more marked than in any other case in this series. The left ankle joint was ankylosed while on the right there was paralysis of the dorsiflexors of the foot and only feeble plantar flexion. Tremor was absent at rest but occurred at the termination of movement, more especially in the left arm. The knee jerks were obtained with difficulty ; ankle reflexes were absent and no response to plantar stimulation was obtained. Appreciation of passive movements was defective at the toes and appreciation of vibration lost at least to the knees. Gait was of the high stepping type.

This appeared to be a case of peroneal muscular atrophy with the addition of nystagmus and slight intention tremor.

Case 8 (VI 40).—This woman was 71 years of age. As a child she is said to have had deformed feet but was otherwise quite normal until about the age of 60. Since then movements of the hands have become clumsy and in the last five years she has noticed weakness of the muscles of both hands.

Examination revealed fine lateral nystagmus to both sides, but the significance of this is perhaps open to doubt as, only a few months earlier, a cataract had been extracted from the left eye. There was wasting in the first interosseous space on both sides similar to that in the other cases, and in the lower limbs bilateral pes cavus. Muscular power, except for weakness of the interossei, was normal, as were the reflexes, although both plantar responses were equivocal. No defect of any form of sensation was found.

The unusual feature of this case is that until the age of 60, probably the only abnormality was the pes cavus, the wasting of the hands having occurred since then.

Case 9 (VI 41).—A woman, aged 70, from about the age of 20 had noticed weakness of the legs, slight unsteadiness in walking, and tremor of the hands. Since then the weakness has increased.

Examination revealed no nystagmus. There was wasting and weakness of the interossei of both hands and a static tremor of the fingers which was increased by movement. Wasting below the knees was marked and there was bilateral pes cavus. All reflexes were present and equal and plantar responses flexor. The only defect found on testing of sensation was loss of appreciation of vibration at least up to the knees.

This seemed to be a typical case of peroneal muscular atrophy with the addition of tremor.

Case 10 (VI 23).—A retired colonel, aged 80, has used toe springs for 30 years. Only a very brief examination was possible. The hands showed wasting of the small muscles ; tremor was absent and coordination normal in the upper limbs. Nystagmus was not observed. Gait was suggestive of bilateral foot drop with some ataxia.

This patient's eldest son (VII 10), a clergyman, undoubtedly suffers from the malady but it is not his parents' wish that I should see him.

The following members of the family were examined and no abnormal signs found :—VI 27 aged 76, VI 37 aged 78, VII 14 aged 35, VII 24 aged 30, VIII 4 aged 11, VIII 5 aged 9, and VIII 6 aged 8.

Distinguished Persons in the Family

One rather unexpected finding in a familial disorder of this nature is the number of distinguished individuals in the eight generations which I have investigated. Those mentioned here are described in the *Dictionary of National Biography* and naval and military biographies and it is highly probable that others achieved fame in their own time.

It is not known which of the two original members introduced the disease. The origin of Elizabeth Heyw—d (I 2) can be traced, according to *Burke's Peerage*, to Peter Heyw—d who was born in 1104. Charles Caldw—l (I 1) was a solicitor in customs in Dublin and came originally from Scotland.

The first affected individual of whom I have any record is II 6. Biographical accounts of two of her brothers are contained in the *Dictionary of National Biography* : II 1 was a barrister and writer, while the other, II 2, was Admiral of the Blue (when the British Navy was divided into two sections, Blue and Red) and was knighted. He retired on account of his health at the beginning of the Napoleonic wars but I have not been able to find whether from this malady or not. Judged by his handwriting in his dispatches to the Admiralty he does not appear to have suffered from tremor.

Many descendants of II 2 are alive and although they have not been directly approached I have not heard of any cases of the malady existing ; one has been created a baronet.

III 3, a knight and a general, became well known after retirement as a writer and reformer, advocating that only a State bank should issue currency—a revolutionary view in the early nineteenth century.

III 6 was knighted and was a general ; in 1813 he drove the Americans from Buffalo and after retiring was Governor of the West Indies.

IV 1 was a scholar and fellow of Jesus College, Oxford.

IV 2 was a Member of the House of Assembly, Jamaica.

IV 8, a Commodore, R.N., was A.D.C. to Queen Victoria and was a C.B.

V 4 was a Doctor of Civil Law and High Sheriff of Dublin.

V 15 was the wife of the naval surgeon referred to earlier whose notes provide the basis of this paper.

V 22 was the wife of an Archbishop of Dublin.

VI 12 was an O.B.E., VI 27 a general, and VI 36 a knight and judge. VI 28 (Case 2) was an admiral and later a clergyman, and VI 23 (Case 10) a colonel. VII 1, was the first baronet.

VII 14 was a captain R.N. at the age of 36, and VII 28 the first baronet.

VIII 8 was a knight and judge.

Longevity

The life span of many members of this family seems to have been longer than might have been expected for the eighteenth and nineteenth centuries, even allowing for their high economic and social status.

The earliest members died at the age of 69 and 60 years. Of the second generation, who lived between 1730 and 1820, four survived to an age of over 70 and one to over 80 years. Excluding two female members (their age is not known) the average duration of life in this generation was 77 years. In the third generation three lived to be over 70 and four to over 80 years. Excluding those killed in the Peninsular War, whose ages are not known (three females and one male), the average age of this generation is 68 years. Three members of the fourth generation (1800–1900) lived to be more than 70, four to be over 80, and one to the age of 94 years of age. Excluding several who died in the first few weeks of life but not those who died before puberty or in battle, the average life span was 62 years (six females are excluded due to inadequate records of their ages).

In the fifth generation, five were over 70 years at death, two over 80, and four over 90. Excluding five who died in the first year and two whose age is not recorded, the average duration of life was 71 years. Two members of this generation are still alive. Of the sixth generation, 24 lived to over 70 and six to over 80, and many of them are still alive.

Variability of the Clinical Features

It was possible to examine most of the living affected members except VII 10 and VII 36 and 37 who may be affected but could not be traced.

The basis of these cases seems to be peroneal muscular atrophy. Extensor plantar responses, which are not a feature of this condition, were found in two cases and nystagmus in three, possibly four cases. Tremor of the hands at rest was observed in three and in several others on activity. Slight cerebellar signs in the upper limbs were present in three. These features are not generally accepted as

TABLE

BLOOD GROUPS OF THE CASES STUDIED

Case	Affected by the Malady	Blood Group								
VI 23	Yes	A2	Ms Ns	P−	R1 R1	Lu (a+)	K+	Le (A−b+)	Fy (a−)	—
VI 25	Yes	A2	Ms Ns	P+	R1 r	Lu (a+)	K+	Le (a−b+)	Fy (a−)	—
VI 27	No	A2	Ms Ns	P−	R1 r	Lu (a+)	K+	Le (a−b+)	Fy (a−)	—
VI 28	Yes	A2	M. S	P−	R1 r	Lu (a−)	K−	Le (a−b+)	Fy (a−)	JK (a+)
VI 37	No	O	MN.S	P+	R2 r	Lu (a−)	K−	Le (a−b+)	Fy (a−)	JK (a−)
VI 38	Yes	O	Ns Ns	P+	R1 r	Lu (a−)	K−	Le (a+b−)	Fy (a−)	JK (a−)
VI 39	Yes	A2	Ns Ns	P+	R1 R1	Lu (a−)	K−	Le (a−b+)	Fy (a−)	—
VI 40	Yes	O	Ns Ns	P+	R1 R1	Lu (a−)	K−	Le (a−b+)	Fy (a+)	—
VI 41	Yes	A2B	Ns Ns	P+	R1 R1	Lu (a−)	K−	Le (a−b+)	Fy (a+)	—
VII 14	No	O	Ms Ns	P−	R1 r	Lu (a−)	K+	Le (a−)	Fy (a−)	—
VII 15	Yes	A2	MS Ms	P−	R1 r	Lu (a−)	K+	Le (a−b+)	Fy (a−)	—
VII 16	Doubtful	A2	MS Ns	P+	rr	Lu (a−)	K+	Le (a−)	Fy (a−)	—
VII 21	Yes	O	Ms Ns	P+	R1 R2	Lu (a−)	K−	Le (a−b+)	Fy (a+)	—
VII 23	Yes	O	MS Ns	P+	R1 R1	Lu (a−)	K−	Le (a+b−)	Fy (a+)	JK (a−)
VII 26	No	O	MN.S	P+	R1 R1	Lu (a−)	K+	Le (a−b+)	Fy (a+)	—
VIII 4	No	O	MS Ns	P−	rr	Lu (a−)	K+	Le (a−b+)	Fy (a−)	—
VIII 5	No	O	MS Ms	P+	rr	Lu (a−)	K−	Le (a−b+)	Fy (a−)	—
VIII 6	No	O	Ms Ns	P−	R1r	Lu (a−)	K−	Le (a−b+)	Fy (a−)	—

Antisera used : anti-A, -A1, -B ; anti-M, -N, -S ; anti-P ; anti-C, -c, -C^w, -D, -E, -e ; anti-Lu^a ; anti-K ; anti-Le^a, -Le^b ; anti -Fy^a and, occasionally, anti-JK^a.

being part of peroneal muscular atrophy but rather of the familial ataxias.

The age of onset of the disease in the cases I saw personally varied as follows :—

Decade	1st	2nd	3rd	4th	6th
Number of Cases ..	3	3	2	1	1

The last of these (Case 8) had deformed feet in childhood although weakness and wasting only developed after the age of 60.

Inheritance

From the family tree it can be seen that 12 affected members produced 22 affected offspring and 33 unaffected (excluding those who died in infancy). The condition is clearly due to a dominant Mendelian character. The penetrance of the gene is incomplete, and, as has been shown in the previous section, its expressivity is variable.

In the case of V 10 it may well be that the difficulty in walking which the patient is said to have had may have been due to another disease as it seems unlikely that the condition could have " skipped " so many generations.

An affected parent was traced except for the Cases VI 39, 40, and 41 where the mother was said to have had " weak feet " but who was not otherwise significantly disabled.

In the literature on this subject, men seem to be three times more frequently affected than women. In this family, however, there is a slight preponderance of females (18 out of 32).

The descendants of III 7 have remained unaffected in spite of intermarriage on several occasions. In the first place III 3 married IV 26, their grandson VI 49 married V 3, and finally VII 32 married IV 30.

The blood groups of the affected members were determined together with those of some unaffected members of the family that I had the opportunity to examine (Table). The blood groups do not give any evidence for or against linkage of their genes with the peroneal atrophy gene.

Summary

In familial disorders of the nervous system variations in the disease from one member to another have been described. The chief interest of this family is that a large number of members have achieved distinction in spite of increasing disability. In addition, they seem to have had an increased expectation of life.

My thanks are due to Dr. Macdonald Critchley for his encouragement in investigating this family. I am indebted to Dr. R. R. Race, of the Medical Research Council Blood Group Research Unit, and Dr. Eliot Slater for criticism and suggestions.

References

Bell, J., and Carmichael, E. A. (1939). " On Hereditary Ataxia and Spastic Paraplegia." *Treas. hum. Inher.*, **4**, Pt. 3, 141.
Bickerstaff, E. R. (1950). *Journal of Neurology, Neurosurgery and Psychiatry*, **13**, 134.
Biemond, A. (1928). *Dtsch. Z. Nervenheilk.*, **104**, 113.
Bogaert, L. van, and Moreau, M. (1940). *Encéphale*, **34** (2), 312.
Boveri, P. (1911). *Münch. med. Wschr.*, **58**, 1238.
Ferguson, F. R., and Critchley, M. (1928). *J. Neurol. Psychopath.*, **9**, 120.
Greenfield, J. G. (1912). *Proc. roy. Soc. Med.* (*Sect. Neurol.*), 5, 75.
Haldane, J. B. S. (1941). *J. Genet.*, **41**, 141, 149.
Hodge, G. (1897). *Brit. med. J.*, **1**, 1405.
Holmes, G. (1907). *Brain*, **30**, 545.
Leeuwen, M. A. van, and Bogaert, L. van (1949). *Ibid.*, **72**, 340.
Marie, P. (1906). *Rev. neurol.* (*Paris*), **14**, 557.
Ross, A. T. (1942). *J. nerv. ment. Dis.*, **95**, 680.
Roth, M. (1948). *Brain*, **71**, 416.
Schut, J. W. (1950). *Arch. Neurol. Psychiat* (*Chicago*), **63**, 535.
——, and Haymaker, W. (1951). *J. Neuropath. clin. Neurol.*, **1**, 183.
Sjögren, T. (1943). *Acta psychiat.* (*Kbh.*), Suppl. 27.
Spillane, J. D. (1940). *Brain*, **63**, 275.
Spiller, W. G. (1910). *J. nerv. ment. Dis.*, **37**, 411.

BOOK REVIEWS

Cough Syncope. By Vincent J. Derbes and Andrew Kerr, Jr. (Pp. viii + 182 ; 7 figures. 34*s*.) Springfield, Illinois : Charles C. Thomas ; Oxford : Blackwell Scientific Publications. 1955.

This book is an extensive monograph on a small but clinically important subject. Cough syncope—the term was coined in this country by Sharpey-Schaefer—refers to the sudden brief attacks of loss or clouding of consciousness, rarely accompanied by a slight convulsion, which may follow a bout of coughing. Laryngeal vertigo and laryngeal epilepsy are alternative and better known names, though the neutral and descriptive term cough syncope is far more satisfactory. The authors review 35 cases of their own, giving brief case histories. They also survey the literature extensively. They confirm once more the consistency of the general clinical setting of these attacks—in the thick-set, middle-aged male who has some mild chronic bronchial or laryngeal affection. They review the physiological mechanisms likely to cause syncope and correlate these with the clinical picture of this syndrome. In general, they favour an aetiology based on cerebral circulatory changes consequent on alteration of intrathoracic pressure, but admit that this may not cover all cases. The 355 references will certainly make the work of value to neurologists and physicians interested in the condition. By some oversight, Sharpey-Schaefer's useful contribution to the mechanics of cough syncope is omitted from the list, though it is referred to in detail in the text.

Stammer is not Nerves : and supplement, **Stammering : Its Cause and Cure.** By H. V. Hemery. (Pp. 67 and 17 respectively.) Published privately by School for Functional Speech Disability, London. 1955.

Many inconvenient motor disorders depend on the habit-forming tendencies of the nervous system taking control in a way that seriously disturbs function. Whatever psychological factors there may be which start this process, the abnormal mechanism becomes physiologically established and largely resistant to psychological treatment. Thus psychological treatment in itself is disappointing in conditions such as stammering, writer's cramp, and spasmodic torticollis.

The writer of these small books on stammering has come to a somewhat similar conclusion on the basis of clinical experience and strongly urges the view that treatment should be by " habit-replacement " in which a different technique for speech is evolved for the patient which will gradually replace his own faulty efforts. This approach is not only successful in practice, but seems to be physiologically sound.

Le Système Nerveux Périphérique. By Guy Lazorthes. (Pp. 348. 214 figures. Fr. fr. 3,500.–.) Paris : Masson. 1955.

This book provides a detailed account of the anatomy, physiology, and clinical methods of investigating disorders of the cranial and spinal nerves. There are over 200 illustrations, most of which are excellent, and they include drawings of the clinical methods of testing the function of individual muscles. The surgical approach to the nerves for division or injection is also considered.

Recent Advances in Neurology and Neuropsychiatry, 6th ed. By Sir Russell Brain and E. B. Strauss. (Pp. x + 311 ; 46 figures. 30*s*.) London : J. & A. Churchill. 1955.

The sixth edition of this publication is an entirely new work and gives a good account of many of the recent advances in knowledge. The subjects covered include the temporal lobes, consciousness, poliomyelitis, demyelinating diseases, the effects of cervical spondylosis, electroencephalography and neuroradiology. Neurologists will find this a useful addition to their library.

Modern Trends in Psychosomatic Medicine. Edited by Desmond O'Neill. (Pp. xi + 375 ; 29 figures. 55*s*.) London : Butterworth. 1955.

If this collection of papers is a fair indication of the present state of psychosomatic medicine, the subject is in a bad way. The faults which have hampered the progress of clinical research are conspicuous in many of the chapters, and the pages expressing therapeutic optimism, conjectures about pathogenesis, and convictions about psychopathology are very numerous in comparison with those recording evidence systematically assembled and strictly analysed. There is, as usual in such collections, a wide diversity of standard between the contributions, ranging from reminiscent and discursive essays to business-like reports of work already published. The first three chapters discuss general issues ; the ensuing four are concerned with paediatric studies ; ulcerative colitis, essential hypertension, thyrotoxicosis, and bronchial asthma are each dealt with in a separate chapter, as are ophthalmic, obstetrical, and dermatological problems ; and in the remaining chapters constitutional aspects, sexual adjustment, muscle tension, music and migraine, group psychotherapy, analytic therapy, and abreaction therapy are considered. The book is not likely, on the whole, to increase respect for this important field of investigation and clinical practice.

Backache. By Frank R. Ober. (Pp. v + 89; 71 figures. 21*s.* 6*d.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1955.

This little book gives a sketchy orthopaedic account of various spinal diseases. There is no serious attempt to discuss the many interesting problems regarding the various mechanisms by which backache can develop.

Wartime Psychiatry: A Compendium of the International Literature. Edited by Nolan C. Davies and Bernice Engle. (Pp. viii + 952. £6.) London: Oxford University Press (Geoffrey Cumberlege). 1954.

This book is a compilation of "most of the important material on psychiatry in World War II". It consists almost entirely of over a thousand abstracts of papers and some book reviews: there is little attempt made to criticize or evaluate the material or to draw conclusions from it. The lack of a subject index further detracts from the book's value.

Graphologie et Physiologie de L'Ecriture. By H Callewaert. (Pp. 168; 53 figures. Fr.fr. 90.–; $1.80.) Louvain: E. Nauwelaerts. 1954.

The author discusses the physiological mechanisms involved in handwriting, and concludes that although this activity reflects certain tendencies of the whole personality, the chief characteristics of a person's writing are determined by the way in which he holds the pen. He refutes the claim that psychological traits can be recognized in individual scripts on the grounds that there is much inconsistency among interpreters and a lack of statistics in their data.

Acta Neuropsiquiatrica argentina

We are glad to welcome the first issue of a new journal concerned with neurology and psychiatry. The first number (Vol. **1**, No. 1) contains 150 pages and is well produced by Dominguez, Bignone y Cia., Buenos Aires.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Cardiovascular Innervation. By G. A. G. Mitchell; Foreword by Sir Geoffrey Jefferson. (Pp. xii + 356; 217 figures. 55*s.*) Edinburgh and London: E. & S. Livingstone. 1956.

Die Kausalgie. By Erich Trostdorf. (Pp. iv + 138; 19 figures. DM. 10.50.) Stuttgart: Georg Thieme Verlag. 1956.

Poliomyelitis, 2nd ed. By W. Ritchie Russell. (Pp. xi + 147; 40 figures. 16*s.*) London: Edward Arnold. 1956.

Clinical Neurosurgery, Volume 2. Proceedings of the Congress of Neurological Surgeons, New York, 1954. (Pp. x + 174; 54 figures. 54*s.*) London: Baillière, Tindall & Cox. 1955.

Acta Neurochirurgica/Supplementum III. 1. Röntgendiagnostiche Probleme bei intrakraniellen Geschwülsten; 2. Elektroencephalographie und Corticographie bei cerebralen Krampfleiden. (Pp. 374; 196 figures. £6 4*s.* 6*d.*; $17.40.) Vienna: Springer-Verlag. 1955.

Selected Works. By I. P. Pavlov, edited by Kh. S. Koshtoyants. (Pp. 654. 10*s.* 6*d.*) London: Central Books. 1956.

Vorträge aus dem Gebiet der klinischen Chemie und Cardiologie. By L. Heilmeyer. (Pp. 96; 70 figures, 10 tables. DM. 10.80.) Stuttgart: Georg Thieme Verlag. 1956.

Das Hirntrauma. By E. Rehwald. (Pp. xii + 528; 106 figures. DM. 44.–.) Stuttgart: Georg Thieme Verlag. 1956.

Diencéfaloshock. By Diego Brage. (Pp. 549; 115 figures. Price not given.) Buenos Aires: Libreria "El Ateneo". 1956.

Practical Neurology. By L. M. Davidoff and E. H. Feiring. (Pp. xvii + 442. 52*s.* 6*d.*) London: McGraw Hill. 1955.

The Neuroses in Clinical Practice. By H. P. Laughlin. (Pp. xlii + 802. 87*s.* 6*d.*) London: W. B. Saunders. 1956.

Die Occipito-Cervical-Gegend. By J. E. W. Brocher. (Pp. x + 145; 91 figures. DM. 48.–.) Stuttgart: Georg Thieme Verlag. 1955.

Clinical Neurology, Vols. 1, 2, and 3. Edited by A. B. Baker. (Pp. 2023; illustrated. 20 guineas the set.) London: Cassell. 1955.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 163.

DIFFUSE DEGENERATION OF THE CEREBRAL WHITE MATTER IN SEVERE DEMENTIA FOLLOWING HEAD INJURY

BY

SABINA J. STRICH

From the Departments of Neurology and Neurological Surgery, Radcliffe Infirmary, Oxford

This paper reports the findings in the brains of five patients who survived a closed head injury in a more or less decerebrate and extremely demented state, for five to 15 months. These cases were selected from a series of patients who died after prolonged coma or other severe disturbances of consciousness following head injury. Both clinically and pathologically they form a distinct group. The head injuries were uncomplicated, that is, there were no fractures of the skull, no intracranial haematomata or lacerations of the brain, and in particular there was no evidence of raised intracranial pressure at any time, yet the patients remained quadriparetic and almost totally unresponsive from the time of the accident. Pathologically the main finding, and one unsuspected from naked-eye appearances, was a diffuse degeneration of the white matter of the cerebral hemispheres.

Few pathological reports of patients with such a degree of post-traumatic dementia have appeared in the literature, partly due no doubt to the fact that until relatively recently few patients with such severe head injuries survived the acute stage. As far as I know only one of the reported cases, that of Rosenblath in 1899, showed extensive degeneration of the white matter, similar to that in our cases, in a patient who survived a closed head injury in a " sleep-like " state for eight months.

Since the findings in our five cases are so similar, a detailed description of the histology and distribution of the lesions will only be given for Case 1.

METHODS USED IN THE INVESTIGATION

The brain and spinal cord were removed in the usual way and fixed by suspension in 10% formol-saline. In Case 5, the brain was perfused *in situ* with bismuth carbonate in formol-saline in order to render the blood vessels radio-opaque. Numerous blocks were taken from each brain and spinal cord and embedded in celloidin or paraffin or used for cutting frozen sections. The staining methods employed were haematoxylin and eosin, haematoxylin and van Gieson, Nissl, Mallory's phosphotungstic acid haematoxylin, and Weil's stain for myelin, on all embedded blocks. Glees' or Holmes' silver methods for nerve fibres, the Prussian blue reaction for iron, and the Holzer technique were carried out on many sections. Frozen sections were used for Bielschowsky's silver impregnation and for staining with Sudan IV, Sudan black, and oil red 0. Much use was made of the Marchi method which was found to give excellent results in these long-standing lesions in spite of very long fixation (nine years in Case 1) in formalin (Smith, Strich, and Sharp, 1956). Since serial sections were not required, a simplified Marchi method was employed: the blocks were washed in tap water for 24 hours and frozen sections 20 to 40 μ thick were cut and placed into Marchi solution as recommended by Glees (1943). After five to seven days the sections were taken out, washed in tap water for several hours, and mounted in glycerine jelly. With this method there is practically no pseudo-Marchi deposit.

TABLE I
CLINICAL DETAILS OF THE CASES

Case	Age in Years	Survival Time in Days	Injuries	Complications		
				Fracture of Skull	Intracranial Haematoma	Other
1 H.B. Male	28	371	Laceration L. forehead and behind L. ear	None	None	—
2 B.S. Female	32	318	L. occipital laceration, bleeding L. ear	None	Subdural film of blood	Tracheotomy
3 G.T. Male	41	257	Lacerations vertex and R. forehead; fracture R. tibia and fibula	None	None	Shock Tracheotomy
4 J.M. Male	27	456	Haematoma R. temple	None	None	Tracheotomy
5 A.T. Female	73	142	Laceration R. forehead; fracture L. femur and clavicle	None	None	—

CASE REPORTS

The ages and survival periods of the patients and details of the injuries will be found in Table I.

Case 1

H. B., a man, aged 28, one year before death was knocked down by a truck and rendered unconscious. Eleven hours later he was still unconscious but responded to painful stimuli by moving all limbs, the left more than the right. Blood pressure, pulse, respirations, and pupillary reactions were normal. There was a laceration on the left forehead, but no skull fractures were seen on radiographs. He lay in the posture which he maintained for the rest of his life, that is, legs strongly extended, the right arm extended at the elbow and internally rotated, and the left arm flexed at the elbow and wrist (*cf.* Case 2, Fig. 18). He moved all limbs feebly, the left less than the right, the tendon reflexes were increased on the left, but the spasticity, which was considerable, was more marked on the right. Both plantar responses were extensor. There was a left facial weakness. These signs remained unchanged for the rest of his life, except that the legs became rigid in flexion towards the end. Extensor spasms affecting all limbs and accompanied by profuse sweating were observed during the first three days.

Biparietal burr holes were made on the eighth day. It was found that the brain was not swollen and the intraventricular pressure was normal.

The patient began to yawn, swallow, and shout on the third day and was soon able to take his diet by mouth, though he could never feed himself. He lay immobile most of the time, becoming restless when disturbed. During the third week he began to open his eyes and a left homonymous hemianopia to menace was demonstrated. The eyes were usually held in conjugate deviation to the right, though he would follow moving objects with them at times. He lay awake most of the day, and though he was very noisy, it is not certain that he ever spoke, and he never obeyed commands. After eight months a slow rhythmic tremor of the right wrist appeared.

The patient eventually became very emaciated and died of bronchopneumonia one year and five days after the accident. He had had no respiratory disturbances or infections throughout his illness, except the terminal bronchopneumonia.

Investigations.—An air encephalogram done four months after the injury showed moderate symmetrical dilatation of the lateral ventricles and some excess of air over the frontal cortex. The cerebrospinal fluid at that time contained 75 mg. protein per 100 ml. and 4 lymphocytes per c.mm.

The clinical diagnosis was dementia with decerebration due to extensive damage in the hemispheres, especially the right.

Post-mortem Findings in Case 1 (P.M. 511/45)

Macroscopic.—The patient was very emaciated. Apart from pleural adhesions and bronchopneumonia the significant abnormalities were limited to the central nervous system. There was no evidence of fracture of the skull and the dura was normal. There was excess of cerebrospinal fluid in the basal cisterns. The brain and its blood vessels looked normal except for a little yellowing of the leptomeninges in the left frontal region. The left hemisphere was cut horizontally, the right coronally. There was moderate dilatation of the ventricles including the third; the aqueduct and fourth ventricle were normal. A few small areas of yellow pigmentation (old haemorrhages) were scattered throughout the white matter and basal ganglia of the hemispheres, and two punctate areas of yellowing were present in the floor of the fourth ventricle. There was yellowing of the roof of the left lateral ventricle and a softening in the left side of the corpus callosum.

Microscopic.—The following description of the lesions applies to all five cases.

The most striking finding is a diffuse and often severe degeneration of the white matter throughout the cerebral hemispheres. There is a marked loss of nerve fibres in the white matter in which compound granular corpuscles containing lipid are scattered, sometimes in very large numbers. The degree of degeneration varies but does not amount to a complete destruction of white matter anywhere, the remaining nerve fibres and their myelin sheaths being apparently normal (Fig. 1). The cellular reaction, apart from compound granular corpuscles, is inconspicuous and consists of a few plump astrocytes, occasional clumps of glial cells or glial stars, and a little " round cell " cuffing of the vessels. There is little fibrous gliosis and no fibrosis. The oligodendroglia looks normal. The lipid in the compound granular corpuscles has the following characteristics: it is in the form of colourless, birefringent crystals which stain faintly or not at all with Sudan IV (Fig. 2) and Sudan black. They stain well with osmic acid (Fig. 3) as used in the Marchi technique, and also with oil red 0. Most of these crystals are clearly intracellular, but long, apparently extracellular crystals can also be seen.

One rather obvious feature in many paraffin and celloidin sections has been the lobulated spaces, bridged by shreds of tissue (Figs. 6, 9, and 20). These spaces have never been seen in frozen sections even when dehydrated and cleared. They are found in areas in which the white matter is abnormal, but they do not correspond with collections of fat granule cells. They may, for example, be seen round the edge of a tract, such as the cingulum, which shows a little degeneration in its centre. These spaces are almost certainly artefacts, but they can be a useful hint to examine carefully the white matter in which they lie, since they may be present even

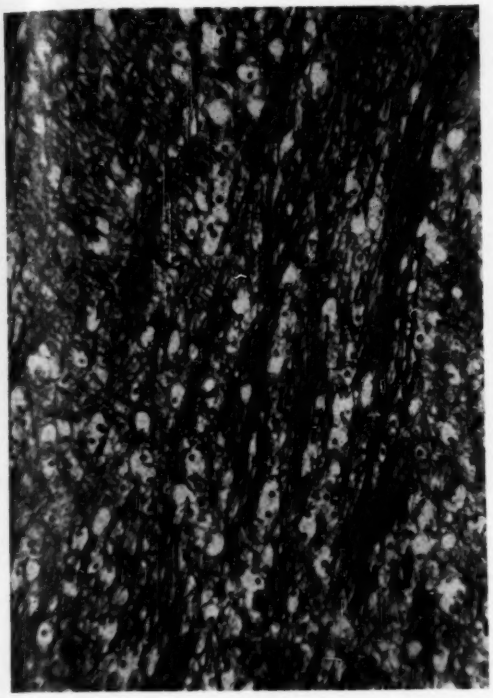


FIG. 1

FIG. 1.—Case 4: White matter from right parietal region showing compound granular corpuscles lying among normal nerve fibres. Glees' silver stain. ×190.

FIG. 2.—Case 4: White matter from right parietal region stained with Sudan IV. Compound granular corpuscles (arrows) can be seen, but their contents are not sudanophilic. ×190.

FIG. 3.—Case 4: White matter from right parietal region, stained by the Marchi technique, showing much lipid. This is contained in compound granular corpuscles. ×190.

FIG. 4.—Case 1: Scar of a small old haemorrhage in the cortex o the insula. Iron-containing macrophages are lying near a blood vessel. Haematoxylin and van Gieson, ×62.

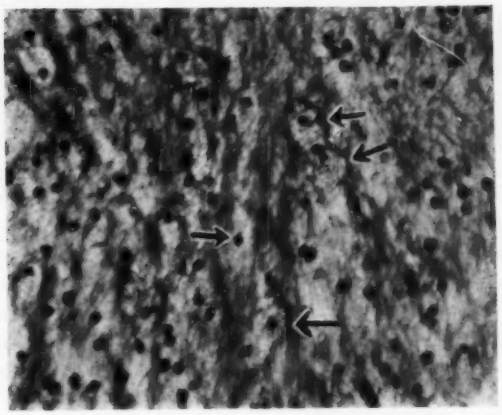


FIG. 2

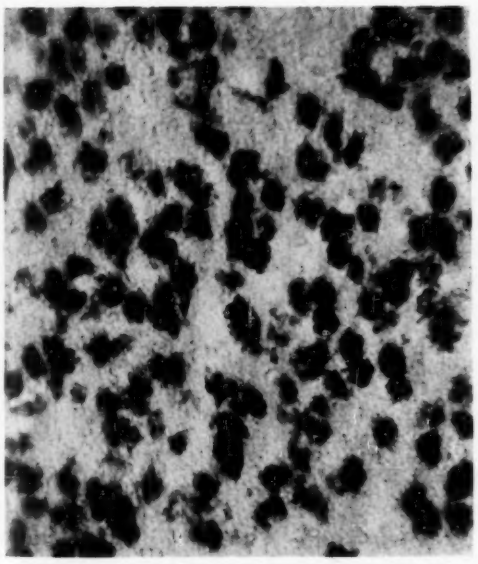


FIG. 3

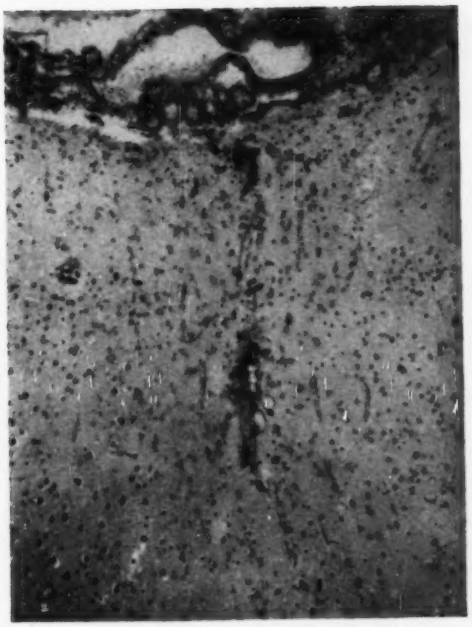


FIG. 4

when there is only slight degeneration (Figs. 8 and 9).

Some small focal areas of complete destruction of white matter due to old haemorrhages or softenings are also found, the haemorrhages being recognizable by the presence of iron-laden macrophages (Fig. 4). In the focal lesions the contents of the fat granule cells differ from those in the diffuse lesion, in that they stain well with Sudan IV and Sudan black, as well as with osmic acid, and this applies to the small amount of fat seen round blood vessels. All the haemorrhages and some of the softenings show fibrosis and all focal lesions are surrounded by a narrow rim of fibrous gliosis.

Lesions in the cortex are few, though three types may be seen. There are healed traumatic contusions affecting the summits of gyri and the outer layers of the cortex (Figs. 19 and 35), small cortical infarcts situated at the bottom or on the side walls of sulci (Figs. 5, 6, and 31), often affecting the deeper cortical layers only, and occasional small haemorrhages (Fig. 4). In general the cerebral cortex looks remarkably normal. In some areas where the lesion of the underlying white matter is severe, there probably is a slight generalized cell loss, but this is nowhere a striking feature. The nerve fibre degeneration could nowhere be traced into the cortex.

The histology and staining reactions of the diffuse white matter lesion are indistinguishable from those of known Wallerian or secondary degeneration in the same brain. Such secondary degeneration can be seen distal to haemorrhages in the white matter and the corpus callosum or in the descending tracts in the brain-stem and spinal cord.

The easiest way to show the degeneration is by the Marchi method, especially in areas where the damage is slight or moderate (Figs. 8 and 9). The lesion can, however, be seen with any stain, though it may have to be looked for with care.

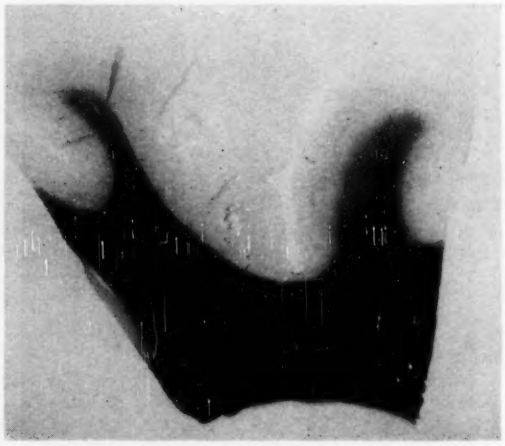


FIG. 5.—Case 1: Right frontal region stained by the Marchi technique. The white matter is full of black-staining products of degeneration. A part of one convolution is spared; notice the sharp line of demarcation between normal and abnormal areas. There is a small cortical softening at the bottom of the sulcus. ×2·2.

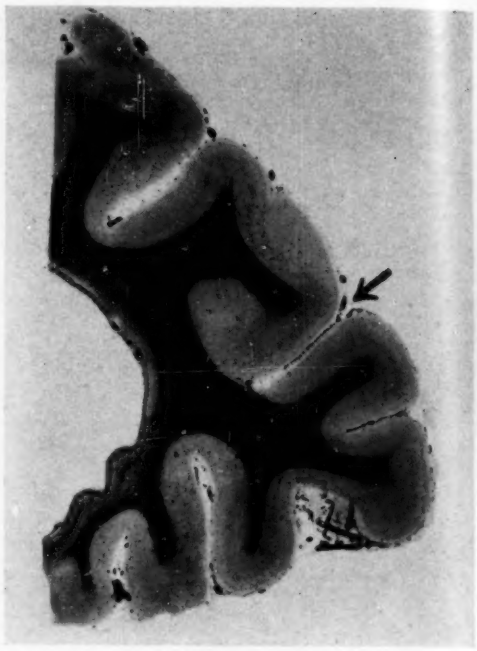


FIG. 6.—Case 1: Right frontal region showing degeneration of the white matter most marked near the ventricle. There is a small softening at the bottom of the sulcus marked with an arrow. The small white spots are not focal lesions but are artefactual spaces which appear in degenerated white matter (see text). Weil, ×1·7.

The blood vessels look normal. Occasional vessels, especially in Case 4, show an increase in perivascular fibrous tissue.

Distribution of Damage in Case 1.—There is a diffuse degeneration of the white matter affecting all parts of the hemispheres. The cerebral cortex is normal, apart from slight cell loss in the frontal region where the white matter damage is most severe, and a few very small cortical infarcts and haemorrhages (Figs. 5 and 6).

The damage in the two hemispheres is about equal in quantity though not in detail of distribution. It is very severe in the frontal poles superiorly and inferiorly (Figs. 5 and 6), moderate in the posterior frontal (Figs. 7, 8, and 9) and parietal regions, and slight in the temporal lobes.

In the occipital lobes (Figs. 10 and 11) marked degeneration is present in the internal and external sagittal strata and there is a little degeneration elsewhere in the white matter, particularly on the right.

In view of the bilateral degeneration, which is only moderate in severity in the region of the motor

FIG. 7

FIG. 8

FIG. 9

FIG. 7.—Case 1: Region of right motor cortex (parasagittal section) showing degeneration products in the white matter. Marchi, ×1·7.

FIG. 8.—Case 1: Region of left motor cortex (horizontal section) showing degeneration of the white matter. The dense staining at the bottom left-hand corner is due to a softening in the corpus callosum. (MC = motor cortex.) Marchi, ×1·7.

FIG. 9.—Case 1: Region of the left motor cortex, block adjacent to that of Fig. 8, stained for myelin. This shows that a diffuse lesion, unless very severe, may be difficult to see with this stain. The completely demyelinated area is a softening in the corpus callosum. The white spots are not focal lesions but are artefacts. (MC = motor cortex.) Weil, ×1·7.

FIG. 10

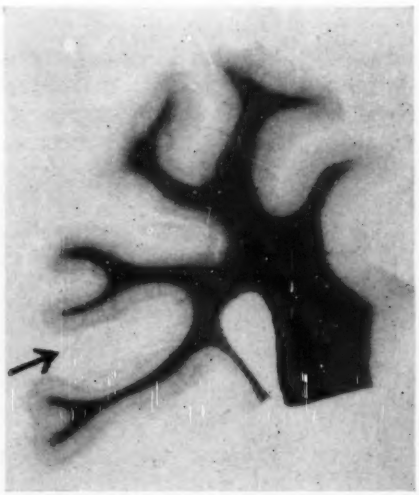


FIG. 11

FIG. 10.—Case 1: Right occipital lobe (coronal section) to show degeneration in the internal and external sagittal strata, and in the white matter including that in the calcarine region (the arrow marks the calcarine fissure). Marchi, ×1·7.

FIG. 11.—Case 1: Left occipital lobe (horizontal section) showing degeneration in the external and internal sagittal strata. There is no degeneration in the calcarine region. (The arrow marks the calcarine fissure.) Marchi, ×1·7.

cortex, it is remarkable that a large number of the fibres which make up the pyramidal tract are interrupted on the right side, whereas almost none are affected on the left, as can be seen in the medulla (Fig. 12). There are no haemorrhages in the internal capsules. Similarly, although the external sagittal stratum is extensively degenerated in both occipital lobes, the fibres of the optic radiation are only affected on the right side, where degeneration can be traced from the lateral geniculate body (Fig. 13) to the calcarine region though not into the visual cortex, which looks normal (Fig. 14). The right lateral geniculate body shows almost complete cell loss, whereas the left is normal (Figs. 15 and 16). Both optic tracts are normal.

Certain peculiarities in the distribution of the white matter degeneration should be noted. In all regions it is particularly well marked near the ventricles (Fig. 6). Occasionally convolutions, or parts of convolutions, look normal, although adjacent parts show marked degeneration, the demarcation between normal and abnormal white matter often being a straight line (Fig. 5). The U-fibres are usually, but not always, spared.

Internal Capsule.—There is severe degeneration in all parts of the right internal capsule, least in the anterior limb. In the left the degeneration is also severe except for the middle portion of the posterior limb which stands out by being almost completely normal.

Thalamus.—This is much shrunken, the different nuclei showing a more or less marked cell loss accompanied by a corresponding degree of gliosis. Numerous compound granular corpuscles are present, particularly in the more heavily myelinated parts. The extent of the damage in the afferent and efferent fibre tracts of the thalamus makes an attempt at exact localization of the degeneration in this nucleus unprofitable, quite apart from the difficulty caused by shrinkage, distortion, and loss of landmarks.

The findings are roughly as follows. On the right there is marked shrinkage of the lateral nucleus and almost complete cell loss in the lateral geniculate body. The anterior and medial nuclei are much better preserved; the centre median nucleus looks normal. On the left the lateral pulvinar, the lateral and the dorsomedial nuclei are severely affected, the medial pulvinar, lateral geniculate body, and centre median nucleus being preserved.

On the whole the nuclei are affected whose efferent or afferent connexions have been interrupted, and it is felt that the thalamic lesions in this and the other cases are secondary to the degeneration of the white matter.

Corpus Striatum.—Except for an occasional small haemorrhage this appears normal. The hypothalamus looks normal.

Degeneration is present in the corpus callosum which has a softening with cyst formation on the left side, in the fornices, in the right mammillothalamic tract, and in the anterior commissure. There are a few fat granule cells in the substantia innominata and in the ansa lenticularis.

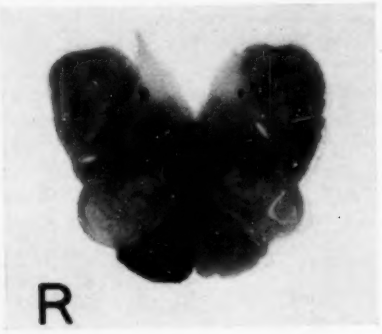
Lower Brain-stem.—Degeneration of the descending tracts can be followed through the brain-stem into the spinal cord, the corticospinal fibres from the left hemisphere being almost completely spared. The degeneration of the descending fibres from the right hemisphere is very marked (Figs. 12 and 17) but not complete; some whole bundles in the pons are unaffected and many normal fibres can be seen in the pyramid.

There is degeneration in the right medial lemniscus (Fig. 17). This begins in the lower pons where it is slight, and gradually becomes more marked as it is traced up. There is also a little degeneration in both central tegmental tracts. No lesion was found which might have accounted for this or the degeneration of the medial lemniscus. There are large numbers of fat granule cells and some gliosis in the left red nucleus; this is due to degeneration in the right superior cerebellar peduncle secondary to a softening. There is some degeneration in the medial longitudinal bundles. There is degeneration superficially at the right border of the upper pons over a short distance.

FIG. 17.—Case 1: Section through the pons to show degeneration of the right descending tracts and the right medial lemniscus. At a lower level the latter is normal. (*cf.* Fig. 12.) Weil, ×2.

The only abnormalities in the medulla are a severe degeneration of the right pyramid and a few fat granule cells in the left (Fig. 12). The nuclei of Goll and Burdach appear normal. The degeneration in the pyramid can be traced down the spinal cord in the crossed and direct pyramidal tracts.

FIG. 12



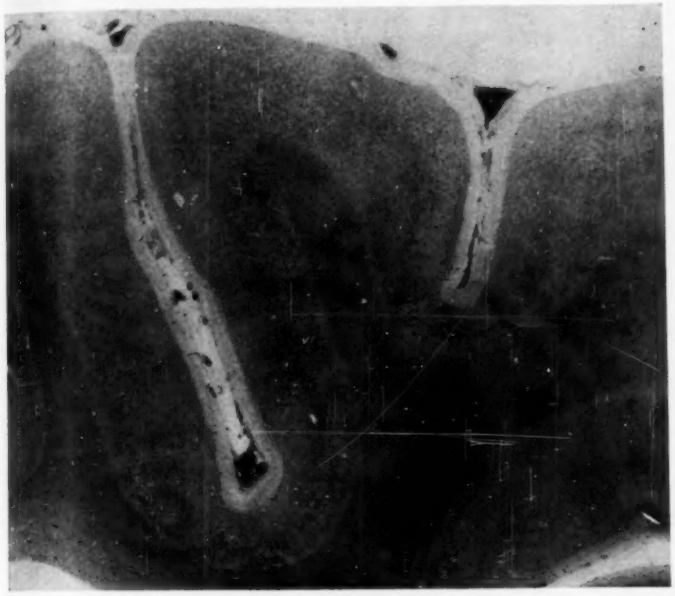


FIG. 14

FIG. 13

FIG. 16

FIG. 12.—Case 1: Medulla, showing severe degeneration in the right pyramid. The left contains a few fat granule cells. The rest of the medulla is normal. Marchi, ×2·4.

FIG. 13.—Case 1: Coronal section through the right lateral geniculate body (LG) showing the degenerated optic radiation leaving it. Marchi, ×2·5.

FIG. 14.—Case 1: Right visual cortex. This looks normal. Nissl, ×4·2.

FIG. 15.—Case 1: Section through the right lateral geniculate body showing almost complete cell loss. Nissl, ×5·4.

FIG. 16.—Case 1: Section through the left lateral geniculate body which is normal. Nissl, ×5·4.

FIG. 15

Cerebellum.—The only abnormality is that more Purkinje cells than normal have swellings (torpedoes) on their axons.

The blood vessels in the brain and the leptomeninges look normal in all areas, but there are very recent, evidently terminal haemorrhages near the lateral ventricles. These are the only evidence of recent pathological changes seen in this brain.

Case 2

B. S., a woman aged 32, a pedestrian, 10½ months before death was run into by a car and was thrown to the ground, hitting her head. The accident was witnessed by an experienced nurse, who stated that the patient became unconscious at once and took up the posture shown in Fig. 18 immediately after landing on the ground. She was seen at the Radcliffe Infirmary within 10 minutes of the accident and was then unconscious. Her blood pressure, respiration, and pulse were normal, the pupils were of equal size (after some days the right became slightly larger than the left) and reacted to light, the corneal reflexes were present. There was a laceration in the right occipital region and abrasions on the left temple. The patient was lying in the attitude which remained characteristic for her (Fig. 18), that is, the head was turned to the right, the eyes deviated to the left, the right arm flexed at elbow and wrist, the left extended and hyperpronated, both legs strongly extended, the feet plantarflexed. She was observed to move the right leg and both arms. The slightest stimulation produced so-called " brain-stem attacks " in which the posture described was accentuated, accompanied by hyperpnoea, salivation, and sweating. No skull fractures were seen on radiographs.

FIG. 18.—Case 2: This shows the characteristic posture of this patient with the left side in the " decerebrate," the right in the " decorticate " attitude. The photograph was taken one month after the accident.

Burr-hole exploration was done on the seventh day. There was a thin film of subdural blood over the right hemisphere, but no evidence of a space-occupying clot, and the ventricular fluid was under atmospheric pressure. The lumbar cerebrospinal fluid, at first blood-stained, returned to normal within three weeks,the highest pressure ever recorded being on the second day, when it was 250 mm. water. Lung infection and respiratory obstruction gave rise to anxiety during the first week and a tracheostomy was made on the eleventh day.

The physical signs remained essentially unchanged until her death. The " brain-stem attacks " subsided after a fortnight. The patient had a quadriparesis, complete in the left leg and more marked in the left arm than the right. All limbs were spastic though the tone varied from day to day; the tendon reflexes were usually brisker on the right, and both plantar responses remained extensor. Later in her illness the patient had attacks of sudden pyrexia with profuse sweating and hyperpnoea, and during these she would look very anxious and frightened.

The patient began to open her eyes after two weeks and soon lay awake for most of the day, sleeping at night. She first spoke definitely after 16 weeks. Five months after the accident she could answer and ask simple questions, showing marked perseveration; she recognized her relatives and was able to count to 10 in English, French, and German. When asked to do anything which was beyond her ability she would shout and scream. She was very moody and although able to take her food by mouth after four months, she refused to eat at times and then had to be tube fed. She remained doubly incontinent.

Her nutritional state remained good; she never menstruated. She developed calcification in many muscles. Her hair, which had been shaved for the exploratory burr-holes, did not grow again until the fifth month, at which time she also showed the maximal improvement in her mental state. This improvement was maintained for about three months after which she became increasingly mute and apathetic. She died quietly 318 days after the accident.

Investigations.—Right and left carotid angiograms were normal.

Ventriculograms made on the 13th and 183rd days showed at first slight, then moderate ventricular dilatation especially of the right temporal horn; the aqueduct and fourth ventricle were normal.

Plasma proteins, serum electrolytes and calcium, and blood urea were found to be within normal limits on numerous occasions.

The clinical diagnosis was " midbrain injury ".

Post-mortem Findings in Case 2 (P.M. 10/52)

Macroscopic.—The patient was a well developed, well nourished young woman. Apart from early bronchopneumonia the internal organs showed no macroscopic or microscopic abnormalities. Many muscles were calcified. There was no evidence of fracture of the skull and the dura was normal.

The brain showed few macroscopic signs of injury, either externally or on coronal section (Fig. 19). There were superficial cortical contusions at the base in the right occipitotemporal region, and a little yellowing of the leptomeninges in relation to the right occipital burr-hole. The lateral and third ventricles were moderately dilated, but the aqueduct and fourth ventricle were normal. There was a softening in the right amygdaloid nucleus and a few

FIG. 19

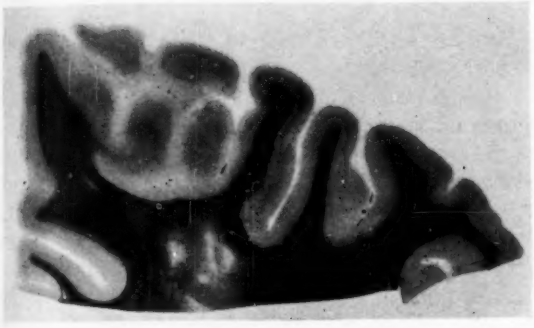


FIG. 20

FIG. 21

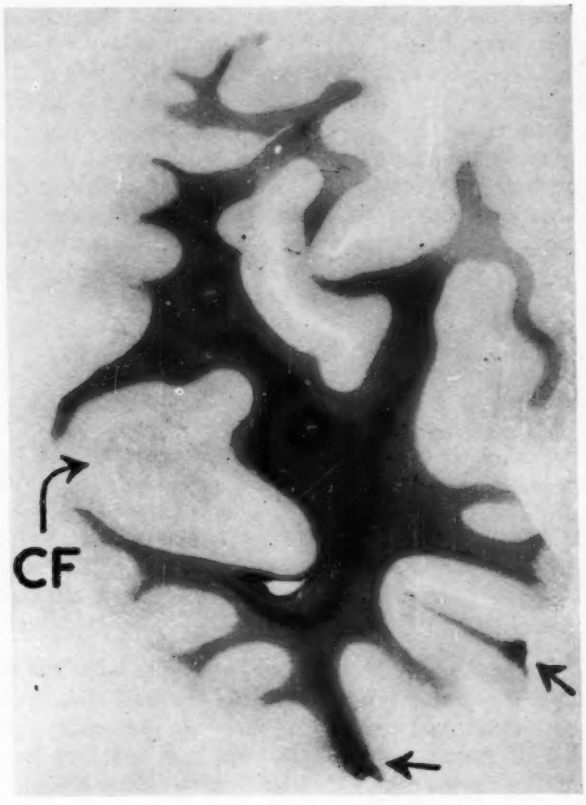


FIG. 22

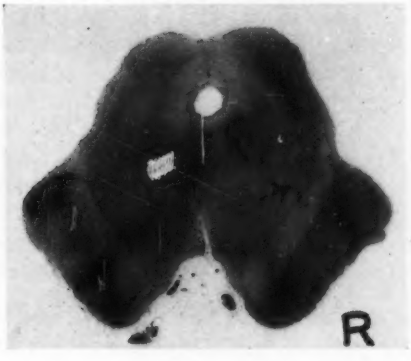


FIG. 23

FIG. 19.—Case 2: Coronal section through the hemispheres. Note the dilatation of the ventricles, the atrophy of the thalami, the superficial contusions on the under surface of the right temporal lobe, and the softening in the right side of the corpus callosum. Otherwise the brain looks normal (*cf.* Figs. 20 and 21).

FIG. 20.—Case 2: Left motor cortex. Section from a block taken from the brain slice shown in Fig. 19. There is severe degeneration of the white matter underlying the motor cortex. Weil, ×1·5.

FIG. 21.—Case 2: Region of the right motor cortex. Section from a block taken from the brain slice shown in Fig. 19. Degeneration products are seen in the white matter. Marchi, ×1·6.

FIG. 22.—Case 2: Coronal section through the right occipital lobe, stained with the Marchi technique. There is degenertion in the external and internal sagittal strata, in the forceps major, and in the rest of the white matter. There are two cortical contusions (arrows). (CF = calcarine fissure.) ×1·5.

FIG. 23.—Case 2: Section of the midbrain showing a small scar in the peri-aqueductal grey matter and another in the right substantia nigra (arrows). There is degeneration in the middle part of the left and the lateral part of the right basis pedunculi. The left medial lemniscus is degenerated but this is difficult to see with this stain. The two dark lines in the left basis pedunculi are due to folds in the section. P.T.A.H., ×1·8.

small foci of yellowing were scattered throughout the white matter and basal ganglia of both hemispheres. An old haemorrhage in the right side of the corpus callosum was also seen. There was a little cortical atrophy. The lower brain-stem appeared slightly shrunken. There were three areas of orange-yellow pigmentation 0·1 to 0·2 cm. diameter in the midbrain and pons. A softening, 0·5 cm. long, was present in the right superior cerebellar peduncle. No abnormality was noted in the spinal cord.

Microscopic.—The findings are as follows:—

Cortex and Underlying White Matter.—No abnormalities were detected in the cerebral cortex, apart from a few small cortical infarcts and the superficial contusions noted macroscopically. The white matter showed severe degeneration (Figs. 20 and 21) throughout most of both hemispheres (see Table II for distribution of degeneration). The optic radiations (Fig. 22) are not involved (*cf.* Case 1) but there are fat granule cells in the left optic tract.

Basal Ganglia: Thalamus.—The dorsomedial nuclei are the best preserved. Compound granular corpuscles, cell loss, and gliosis are present in the lateral nucleus, the anterior nucleus, and are less marked in the pulvinar of both sides. These changes are more marked on the left. The lateral geniculate bodies are normal.

The *corpus striatum* shows a few small old haemorrhages. There are pseudo-calcareous deposits and some extracellular fat in the globus pallidus. There is a softening in the right amygdaloid nucleus going into the uncus. The hypothalamus looks normal.

Small haemorrhages and softenings, rather more numerous than in Case 1, are seen throughout the areas of affected white matter including both internal capsules. They are not, however, considered sufficient to account for the degree of degeneration.

Lower Brain-stem and Spinal Cord.—The degeneration in the descending tracts affects the cortico-spinal fibres on the left much more than on the right, and it can be traced into the spinal cord. The fronto- and temporo-pontine fibres are more affected on the left. Other tracts affected are shown in Table II. Serial sections through the pons failed to show any lesions to account for the degeneration of the medial lemnisci, the central tegmental tracts, or the medial longitudinal bundles.

There is a little gliosis in the sensory nucleus of the right fifth nerve and a few compound granular corpuscles are in the mesencephalic root of the right fifth nerve. There is a little superficial damage at the

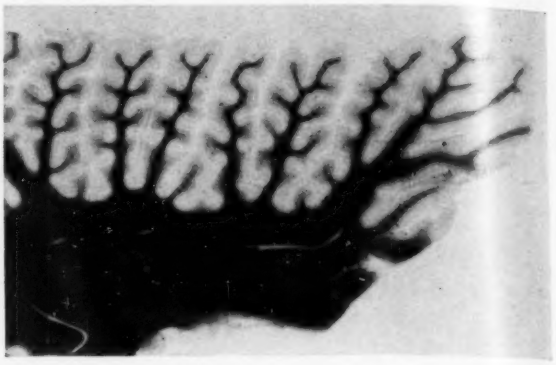


FIG. 24.—Case 2: Left cerebellum showing degeneration in some of the folia and of the fibres in the neighbourhood of the dentate nucleus. Marchi, ×2.

right upper border of the pons, where the transverse pontine fibres show some degeneration.

There is an old haemorrhage in the pontine tegmentum just lateral to the left medial longitudinal bundle, and two glial scars in relation to medium-sized blood vessels, one in the right substantia nigra, the other in the right peri-aqueductal grey matter (Fig. 23). The whole peri-aqueductal region and the superior colliculi appear more cellular than normal.

In the floor of the fourth ventricle and throughout the pons there are small, very recent, evidently terminal haemorrhages. These are the only evidence of recent pathological changes seen in the brain.

Cerebellum.—The white matter is a little thinned and material staining with Marchi is seen in some folia and near the dentate nucleus (Fig. 24).

Blood Vessels.—These were examined with care and no abnormality was found in them.

Case 3

G. T., a man aged 40, eight months before death was knocked off his bicycle and immediately became unconscious. He sustained a compound fracture of the right tibia and fibula, and several lacerations of the vertex of the head and the left forehead from which he was bleeding when seen at the Radcliffe Infirmary one and a half hours after the accident. The patient was then still deeply unconscious, barely responding to painful stimuli. He was severely shocked, the blood pressure being 60/30 mm. Hg, but this rose to normal after blood transfusion. By the next day pulse, respirations, and pupillary reactions were normal, the corneal reflexes were present, and both plantar responses were extensor.

Lumbar puncture on the third day showed a slightly blood-stained fluid under normal pressure. For the first four days the patient was very ill because of atelectasis and infection of both lungs and a tracheotomy was performed 24 hours after the accident. He lay motionless and unresponsive for many weeks, hardly moving his

FIG. 25

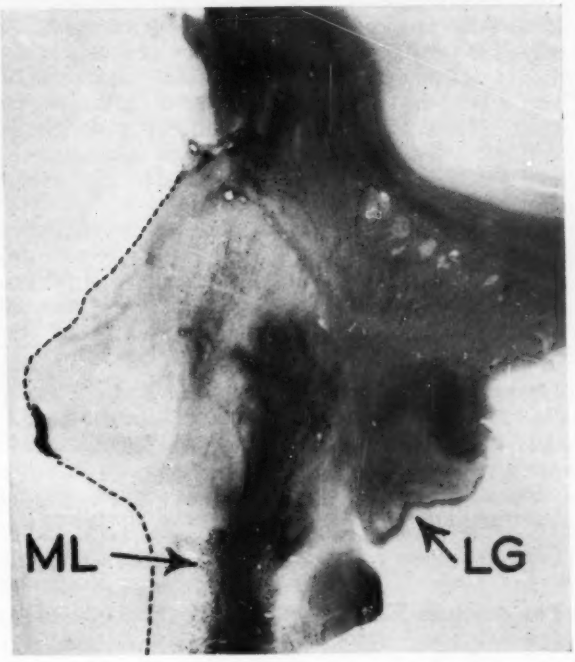


FIG. 27

FIG. 26

FIG. 28

FIG. 25.—Case 3: Coronal section through the hemispheres showing slightly dilated ventricles, atrophy of the thalami, and a softening in the left side of the corpus callosum. The brain looks normal otherwise.

FIG. 26.—Case 3: Section from the left parietal region of the brain slice in Fig. 25, showing degeneration products in the white matter. Marchi, ×1·5.

FIG. 27.—Case 3: Coronal section through the right thalamus and lateral geniculate body stained with the Marchi technique. The

FIG. 27 (*cont.*)—degenerated medial lemniscus can be seen entering the ventral postero-lateral nucleus of the thalamus. There is degeneration in the postero-lateral nucleus and in the rostral stalk (above). Note that the compound granular corpuscles lie in rows. (LG = lateral geniculate body; ML = medial lemniscus. The dotted line represents the outline of the thalamus.) ×2·5.

FIG. 28.—Case 3: Section through the medulla to show the degeneration of the right pyramid, the arcuate fibres, and the central tegmental tracts (lateral and posterior to the inferior olives). Weil, ×2.

limbs even to painful stimuli (the right leg was in plaster).

After three weeks he began to open his eyes; after seven weeks he was able to obey simple commands, but only used the right hand for voluntary actions. At this time it was thought that the tendon reflexes on the left were a little increased and that the left leg was slightly spastic. Eleven weeks after the injury the patient began to speak a few words and was able to take semi-solid food by mouth slowly. His response to pain always remained sluggish.

This patient became extremely wasted and developed bed sores in spite of an adequate diet and expert nursing care. He developed oedema of the hands for which no cause was found and also calcification in many muscles. He died of bronchopneumonia 250 days after the accident.

Investigations.—Ventriculograms five and 18 weeks after the accident showed first slight, then moderate, ventricular dilatation. The aqueduct and fourth ventricle were normal.

Repeated estimations of plasma proteins, serum electrolytes and calcium, and blood urea were normal.

The clinical diagnosis of brain-stem injury was made.

Post-mortem Findings in Case 3 (P.M. 218/53)

Macroscopic.—The body was very emaciated and had several bed sores. The left knee was fixed in semiflexion and there was a healed fracture of the right lower leg. There was calcification of many muscles. Well-marked bronchopneumonia and a small stone in the left kidney were the only abnormalities found in the internal organs.

There was no evidence of fracture of the skull, and the dura, venous sinuses, and blood vessels at the base of the brain were normal.

No external abnormality of the brain was noted. Coronal sections showed moderate dilatation of the lateral and third ventricles (Fig. 25). There was a yellow softening in the left side of the corpus callosum, a little yellowing of the right uncus, a small area of yellowing in the right thalamus, and one in the left parietal region.

The aqueduct was slightly dilated and there were a few old softenings 0·1 to 0·2 cm. diameter in the tegmental region of the midbrain.

Microscopic.—The findings are as follows :—

Cortex and Underlying White Matter.—The cortex looks normal in all areas examined. Degeneration of the white matter (Fig. 26) is well marked (see Table II), and on the whole is more severe in the left hemisphere (*cf.* descending tracts).

A small softening abuts on the lateral part of the posterior limb of the right internal capsule.

Basal Ganglia: Thalamus.—The dorso-medial, anterior and centre median nuclei, and the right pulvinar appear more or less normal. All other regions show cell loss with gliosis and fat granule cells (Fig. 27).

Corpus Striatum.—This contains a few small, old haemorrhages. There is slight gliosis of the left globus pallidus and a superficial softening of the right uncus. The hypothalamus looks normal.

Lower Brain-stem.—In spite of the fact that the damage in the left hemisphere is more severe than that in the right, the corticospinal fibres are only degenerated on the right, being almost completely spared on the left (Fig. 28). On the left the fronto-pontine tract only is affected. At the upper end of the pons there is degeneration at the right lateral margin of the brain-stem.

This case shows more old brain-stem haemorrhages than the others. There is one about 0·3 × 0·2 and 0·5 cm. long, and three smaller ones in the tegmental region of the midbrain, one 0·2 cm. diameter, and several very small ones in the basal part of the pons, and one in the left superior cerebellar peduncle.

Spinal Cord.—Many anterior horn cells show chromatolysis. There is degeneration in the left lateral and right anterior columns.

Cerebellum.—There is a slight loss of Purkinje cells. A little degeneration can be seen in the white matter of some of the folia and round the dentate nucleus.

Case 4

J. M., a man aged 27, was involved in a road accident 15 months before death. When seen an hour later he was comatose and the pupils although small and equal did not react to light. He improved steadily and two hours after the accident, though still unconscious, he responded to painful stimuli, and blood pressure, pulse, respirations, and pupillary reactions were normal. There were abrasions on the right ear and a haematoma on the right temple and the right shoulder. Four hours after the injury he inhaled some vomit which caused severe respiratory distress for some

FIG. 29.—Case 4: This shows the patient during one of his "decerebrate" or "brain-stem" attacks. The picture was taken six weeks after the accident.

FIG. 30.—Case 4: This shows the same patient as in Fig. 29. He is here seen awake and lying in his usual posture. Photograph taken five months after the accident.

minutes. His general condition deteriorated after this and he began to have attacks of decerebration (Fig. 29) accompanied by raised blood pressure. Exploratory burr holes were made 12 hours after the accident, when it was found that the brain looked normal, that the intraventricular pressure was not increased but that the cerebrospinal fluid was lightly blood-stained. The patient then passed through a period of hyperthermia which was controlled with an iced water rectal drip. Repeated lumbar punctures showed that, although the pressure was usually normal, on one occasion 48 hours after the accident it was 400 mm. water. On the fourth day the patient opened his eyes and groaned in response to pain. Both lungs, however, showed evidence of consolidation and he was frequently cyanosed. It was not until a tracheotomy was made on the tenth day that the chest infection was brought under control. On the ninth day ventriculography was carried out to exclude a space-occupying lesion. The intraventricular pressure was somewhat increased (the patient's respirations were very laboured at the time) but the ventricles showed a slight symmetrical dilatation and there was no evidence of an intracranial clot.

After three weeks the patient lay in the attitude shown in Fig. 30, with feet plantar flexed, legs extended, arms flexed; the tone in the limbs was normal except at the ankles where it was much increased. He lay with his eyes open most of the time, following moving objects round the room; he yawned, swallowed, and grimaced in response to pain, when it was seen that there was no facial weakness. A little later it was said that he distinguished between people he liked and those he disliked. At this time he began to use the left hand voluntarily, but not the right. This relative improvement was accompanied by an increase in spasticity of all limbs more marked on the right. He still had occasional "brain-stem attacks" lasting up to two hours in which he assumed a decerebrate posture accompanied by profuse sweating and a high blood pressure (Fig. 29). He never spoke or obeyed commands. After six months he was transferred to another hospital where he died, having become rather thin, 450 days after the accident.

Ventriculograms.—On the ninth day there was very slight ventricular dilatation. After 12 weeks there had been a slight increase in the size of the lateral and third ventricles. The appearances were unchanged after 28 weeks.

Post-mortem Findings in Case 4 (P.M. 464/50)

Macroscopic.—The body was emaciated. Except for bronchopneumonia the internal organs were normal. There was no evidence of fracture of the skull; the dura and venous sinuses were normal. The cerebral hemispheres looked normal externally, though the pons and medulla were slightly shrunken, particularly on the left. The cerebellum was markedly wasted and firmer than normal. The blood vessels at the base of the brain were normal.

The occipital and frontal lobes were cut coronally, the rest of the brain horizontally. There was slight ventricular dilatation. Areas of yellowing were present in the posterior part of the corpus callosum on the right, with yellowing of the roof of the right lateral ventricle; there were streaks of yellow pigmentation in the white matter of the right temporal lobe, a superficial softening in the right uncus, a few small areas of yellowing in cortex and white matter, particularly in the parietal regions, and a cyst, 0·3 cm. diameter, in the right caudate nucleus. There was a similar cyst in the white matter of the left cerebellar lobe. The lower brain-stem showed a few minute yellow areas in the right tegmental region.

Microscopic.—The following are the main findings:—

Cortex and Underlying White Matter.—In general the cerebral cortex looks normal. There are a number of small cortical infarcts, rather more numerous than in the other cases, each confined to the bottom of a sulcus (Fig. 31), often affecting the deeper layers of cortex only. There is probably a slight cell loss in areas where the underlying white matter is much damaged. Ammon's horn is normal on both sides.

The white matter lesion (Fig. 31) is very severe in this case (see Table II), although some convolutions and the left frontal pole are spared. There is a

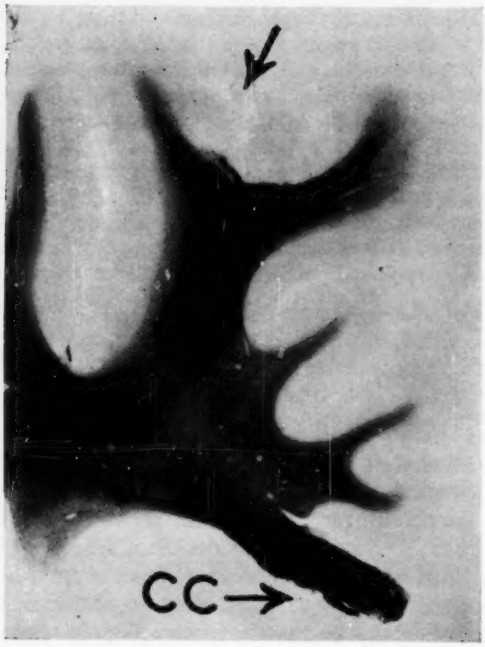


FIG. 31

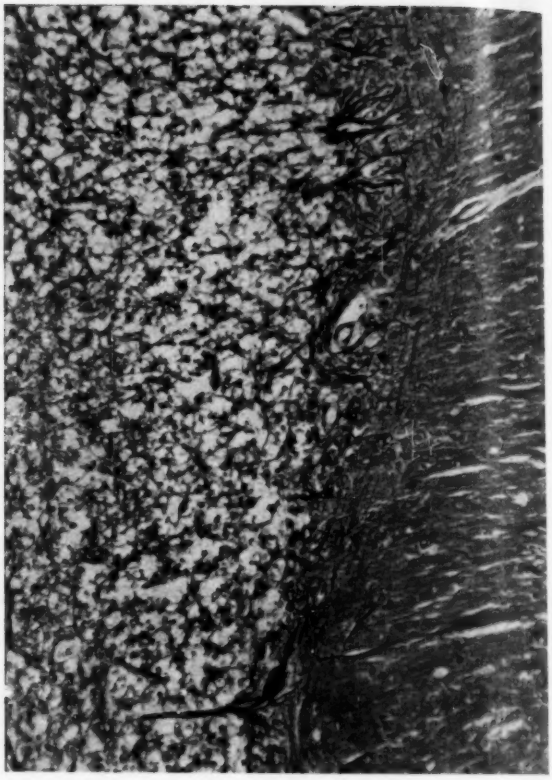


FIG. 32

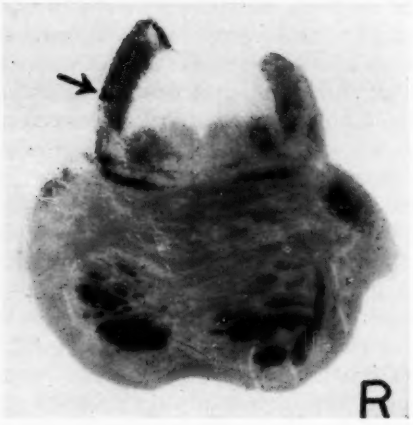


FIG. 33

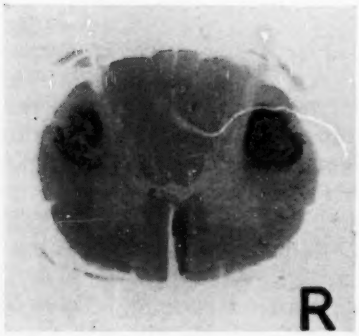


FIG. 34

FIG. 31.—Case 4: Right parietal region stained with the Marchi technique. There is well-marked degeneration of the white matter, sparing the two convolutions above the corpus callosum (CC). This is severely degenerated. A cortical infarct is seen at the bottom of one sulcus (arrow). ×2·4.

FIG. 32.—Case 4: Section of the cerebellum. There was an almost total loss of Purkinje cells. This section shows a " torpedo " and several " empty baskets ". Glees' silver stain, ×153.

FIG. 33.—Case 4: The pons stained with the Marchi technique. There is degeneration in the descending tracts, the fifth nerves, the medial lemnisci, the lateral lemnisci, the central tegmental tracts, the superior cerebellar peduncles, and a bundle of transverse fibres. Notice that the fat granule cells still lie neatly in their tracts, although the injury occurred 15 months before death. Apart from a haemorrhage (arrow) in the left superior cerebellar peduncle there were no haemorrhages or softenings in midbrain, pons or medulla. ×2·1.

FIG. 34.—Case 4: Spinal cord showing degeneration in both crossed and the right uncrossed pyramidal tract. Marchi, ×3·75.

softening, about 0·5 cm. diameter, in the posterior third of the left internal capsule, just before it enters the basic pedunculi.

Basal Ganglia.—There are marked changes in the thalami, particularly in the lateral and ventral nuclei, leaving the anterior and dorsomedial nuclei, the posterior part of the pulvinar, and the lateral geniculate bodies almost normal. The corpus striatum contains a few old haemorrhages. There is a slight gliosis in the left globus pallidus. The hypothalamus looks normal.

Cerebellum.—There is an almost total loss of Purkinje cells except in the vermis. Many of the remaining cells show swellings (torpedoes) on their axons (Fig. 32). There is a marked proliferation of Bergman cells. The white matter is demyelinated, and in Marchi preparations compound granular corpuscles are seen in the white matter of the folia where they are collected opposite the sulci of cerebellar cortex; in the central white matter they are found chiefly surrounding the dentate nucleus, which shows cell loss and gliosis.

Lower Brain-stem.—The degeneration of the descending tracts is considerably less severe on the right where some bundles are quite normal. Marchi preparations of the pons (Fig. 33) show the affected tracts which are also listed in Table II. The degeneration in the medial lemnisci is present from the upper medulla upwards. There is slight gliosis in the gracile and cuneate nuclei, in the sensory nuclei of the fifth nerves, and in the substantia nigra. There is marked cell loss and gliosis in the inferior olives. Some of the transverse bundles of pontine fibres are degenerated (Fig. 33). The surface of the inferior colliculi shows evidence of old haemorrhage and there are a few iron-containing macrophages in the basal part of the pons.

Spinal Cord.—There is degeneration in the right and to a less extent the left lateral columns; the anterior column is degenerated on the left side only (Fig. 34).

Case 5

A. T., a woman, aged 73, a pedestrian, was knocked down by a motor cycle five months before death. When first seen shortly after the accident, she was unconscious, but moved the right arm in response to painful stimuli, and shortly afterwards all four limbs. The blood pressure was 130/90 mm. Hg, which was normal for her; pulse, respiration, pupillary reactions, and corneal reflexes were normal. She had a laceration on the right forehead and had fractured the left clavicle and the left femur. The limbs were flaccid. The patient gradually reacted more to painful stimuli, the right limbs moving better than the left. On the seventeenth day the tone of the right limbs was found to be increased, though the tendon reflexes were equal on the two sides. She lay immobile most of the time. On the tenth day she began to open her eyes and on the 74th day she first spoke definitely, though her vocabulary remained limited to a few words. She was able to obey simple commands. She was doubly incontinent and required tube feeding throughout her illness. The left shoulder was subluxated and she developed calcification in the surrounding muscles. Her state of nutrition remained good, but she developed sacral bed sores and died of bronchopneumonia 142 days after the accident.

Investigations.—Lumbar puncture on the fourth day and on several subsequent occasions showed a normal cerebrospinal fluid pressure. A right angiogram made on the 35th day was normal.

Post-mortem Findings in Case 5 (P.M. 271/49)

Macroscopic.—The body was well nourished; there were small bed sores on both heels and a large one over the sacrum. There was a large callus in the middle of the shaft of the left femur and on the left clavicle. There was tracheitis and hypostatic pneumonia in both lungs. There was an old perinephric haematoma near the right kidney.

There were no fractures of the skull and the dura was normal.

The brain was injected *in situ* with bismuth bicarbonate in formalin, via the carotid arteries. This produced marked swelling of the brain, particularly of the right hemisphere. Radiographs of the brain made afterwards showed normal vessels.

There was a translucent membrane, 5 cm. diameter, over the left frontal lobe, probably the remains of a thin subdural haematoma. The vessels at the base of the brain were healthy. The size of the ventricles could not be judged because of the artefactual brain swelling. The only abnormality noted on the coronal sections was a cortical contusion in the right parietal region. The brain-stem and spinal cord were normal, except for minute flecks of yellowing in the left superior cerebellar peduncle.

Microscopic.—The injection mass made the cutting and interpretation of celloidin and paraffin sections difficult. The Marchi method was found to give the most satisfactory preparations for examination.

Cortex and Underlying White Matter.—Except for the contusion in the right parietal region which was noted macroscopically, the cortex appears normal in the areas examined. This contusion occupies the summit and side walls of the convolution (Fig. 35). There are softenings in Ammon's horn on both sides. The white matter shows severe degeneration in most areas (Table II and Fig. 35). Occasional retraction bulbs and abnormal nerve fibres are seen in the

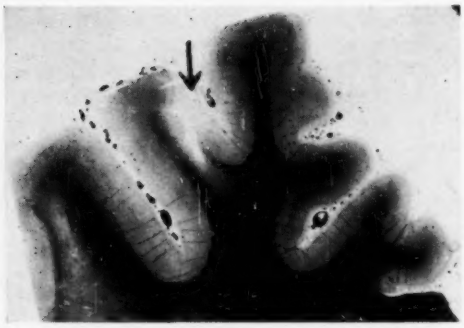


FIG. 35

FIG. 36

FIG. 37

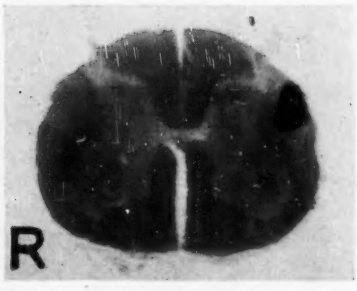


FIG. 38

FIG. 35.—Case 5: Right parietal region showing degeneration of the white matter and the only cortical lesion (arrow) found in this brain. The small white spots are not focal lesions but artefacts occurring in abnormal white matter. Weil, ×1·7.

FIG. 36.—Case 5: Medulla showing degeneration in the decussating pyramids. Marchi, ×3·8.

FIG. 37.—Case 5: Spinal cord in the cervical region showing unequal degeneration in the crossed and direct cortico-spinal tracts. The black spots in the anterior horns are due to staining of the lipochrome in the nerve cells. Marchi, ×3·8.

FIG. 38.—Case 5: Spinal cord in the lumbar region. There is degeneration in the left cortico-spinal tract. The degeneration in the right anterior and lateral columns has petered out. (*cf.* Figs. 36 and 37.) Marchi, ×3·8.

right parietal region, in areas where there is no obvious focal damage.

Basal Ganglia: Thalamus.—The picture is difficult to interpret, but there appear to be fat granule cells and gliosis in the lateral nuclei and the pulvinar, right more than left. The lateral geniculate bodies are normal. The corpus striatum and hypothalamus look normal.

Lower Brain-stem and Spinal Cord.—Degeneration of the cortico-spinal tracts is very much worse on the right (Fig. 36, 37, and 38). The fronto-pontine fibres are affected on the left. For degeneration of other tracts see Table II.

Cerebellum.—There is some degeneration of the white matter of the folia of the upper half of the cerebellum and of the peridentate fibres, on both sides.

SUMMARY OF THE FINDINGS

Five patients, four under 40 and one 73 years old, received closed head injuries without fracture of the skull which rendered them unconscious immediately. Within a few hours of the accident blood pressure, respiration, and pupillary reactions were normal, but there were more or less marked signs of pyramidal tract involvement on one or both sides. Three of the patients were subject to attacks of decerebration with rise in blood pressure and sweating. None of the patients developed significant intracranial haemorrhages or showed clinical evidence of oedema. Three required tracheotomies. The patients did not recover normal consciousness but remained almost completely unresponsive, though they lay awake for most of the day; they were in fact extremely demented. All patients had a more or less spastic quadriparesis. In this state they survived for five to 15 months.

The significant pathological features were. The brain looked normal macroscopically apart from dilated lateral and third ventricles. Microscopically there were a few small softenings and haemorrhages and a diffuse degeneration of the white matter

characterized by loss of nerve fibres and the presence of numerous compound granular corpuscles. The cerebral cortex was normal. There was secondary atrophy of the thalamus and asymmetrical degeneration in the long descending tracts. There was degeneration in the medial lemnisci and the central tegmental tracts, but no lesions were found to account for this. The main fibre tracts affected and the external marks of violence are summarized in Tables II and III. In addition there was degeneration in the anterior commissure, the fornices and the mammillo-thalamic tracts, and in the white matter of the cerebellum. Three cases had very small, old haemorrhages in the lower brain-stem. All cases had lesions in the corpus callosum and in one or both superior cerebellar peduncles.

TABLE II

DISTRIBUTION OF THE DEGENERATION IN THE FIVE CASES

		Case 1	Case 2	Case 3	Case 4	Case 5
Cerebral White Matter						
Frontal pole	R.	+++	+	0	0	+
	L.	+++	0	+	0	+
Posterior	R.	++	++	++	+++	—
	L.	++	+++	++	+++	+
Parietal	R.	++	++	++	+++	+++
	L.	++	++	++	+++	++
Temporal	R.	+	++*	0	++	—
	L.	+	+	+	—	—
Occipital sagittal strata	R.	+++	++	+	+	+
	L.	+++	++	+	+	+
Optic radiation	R.	+++	0	0	0	0
	L.	0	0	0	0	0
Elsewhere	R.	+	+	0	0	0
	L.	0	0	0	0	0
Tracts						
Internal capsule Anterior limb	R.	++	++	++	++	0
	L.	+++	++	++	+++	0
Posterior limb	R.	++	++	+++	++	++
	L.	0	+++	++	+++	+
Retrolenticular	R.	+	+	+	++	+
	L.	++	++	+	+++	+
Corpus callosum	R.	+++	+++h	+++	+++h	++
	L.	h		h		
Anterior commissure		+	+	?+	+	+
Fornix	R.	+	+	+	+	?+
	L.	0	+	0	+	?+
Mammillo-thalamic tracts	R.	+	+	0	+	+
	L.	0	+	0	+	0
Cortico-spinal tract	R.	+++	+	+++	++	+++
	L.	0	+++	0	+++	+
Medial lemniscus	R.	++	+	++	++	+++
	L.	0	+++	+	+++	+
Superior cerebellar peduncle	R.	++h	+++h	+	+	+
	L.	0	+	++h	+++h	++h
Central tegmental tract	R.	+	+	++	++	+
	L.	+	0	++	++	0
Medial longitudinal bundle	R.	+	+	+	0	+
	L.	+	+	+	0	+
Fifth nerve	R.	0	+	+	+	0
	L.	0	0	+	+	0
Lateral lemniscus	R.	0	+	0	+	0
	L.	0	0	0	++	+
Spinal cord lateral column	R.	0	+++	0	+++	+++
	L.	+++	+	+++	++	+
Anterior column	R.	++	+	++	++	+
	L.	0	++	0	0	++
Elsewhere		0	0	0	0	0
Basal Ganglia Thalamus	R.	+++I	++	+++	+++	++
	L.	++	+++	+++	+++	++
Corpus striatum	R.	0	0	0	0	0
	L.	0	0	0	0	0
Hypothalamus	R.	0	0	0	0	0
	L.	0	0	0	0	0
Ammon's horn	R.	0	0	0	0	└†
	L.	0	0	0	0	+
Cerebellum		0	+	+	+++H	+

* = Cortical contusion
h = Haemorrhage
I = Left lateral geniculate body degenerated
† = Bilateral necrosis
H = Total loss of Purkinje cells

+++ = Severe degeneration
++ = Moderate degeneration
+ = Slight degeneration
0 = No degeneration
— = Not examined

DISCUSSION

Interpretation of Histological Findings

During the months which our patients survived the head injury, healing processes will have been occurring in the damaged brain and therefore the relation of the histological findings to the original damage will have to be discussed.

One of the surprising pathological features is the presence of so much lipid material at the time of death, and one has to consider whether the lesions now seen can have been produced near the time of the accident or whether there has been progressive pathological change. It is impossible to date pathological lesions with any accuracy and one can only say that all the lesions, whether focal or diffuse, look old and quiescent and of the same age, with the exception of very recent (terminal) haemorrhages. The fact that the breakdown products stain with the Marchi method even after long fixation in formalin can be taken to indicate that these lesions are at least several months old, since it has been shown by Smith (1956) that Marchi-positive material from recent lesions disappears on storage in formalin. Since, in addition, there is no clinical evidence of increase of neurological abnormalities it is likely that the damage found in these brains occurred at or near the time of the accident.

It seems also that very little distortion of the original picture has come about through migration of macrophages containing degeneration products into healthy regions. This is clear from the study of such areas as the brain-stem or the stalks of the thalamus where fat granule cells still lie in the tracts whose degeneration they represent, often in neat rows parallel to the fibre direction of the tract (Figs. 27 and 33).

Some of the breakdown products from the diffuse lesion have probably been absorbed, though much is clearly left. It is unlikely that any of the focal lesions have completely disappeared, as scars of very small haemorrhages and softenings are still visible (Fig. 4).

TABLE III
THE PYRAMIDAL SIGNS AND THE SITE OF INJURY AND OF ASYMMETRICAL LESIONS

Case	External Injuries	Motor Signs	Pyramid	Degeneration or Haemorrhage in: Medial Lemniscus	Corpus Callosum	Superior Cerebellar Peduncle	Other Regions
1	L. forehead, behind L. ear	Paralysis L. > R. Spasticity R. > L.	R.	R.	L.	R.	R. optic radiation
3	Vertex L. forehead	Paralysis L. > R. Spasticity L. > R.	R.	R.	L.	L > R.	R. uncus Fifth nerves
5	R. forehead	Paralysis L. > R. Spasticity L. > R.	Mainly R.	Mainly R.	Midline Splenium	L. Slight R.	L. lateral lemniscus
2	R. occipital	Paralysis L. > R. Spasticity R. > L.	Mainly L.	Mainly L.	R. and Midline Splenium	R. > L.	L. optic tract R. uncus inferior surface of R. temporal lobe
4	R. temple	Paralysis R. > L. Spasticity L. > R.	L. > R.	L. > R.	R.	L. > R.	R. uncus Fifth nerves Lateral lemnisci

It is therefore concluded that the lesions seen at necropsy correspond fairly closely to the original lesions.

Pathogenesis of Lesions

This is not known, but evidence will be presented for the suggestion that distortion of the brain by mechanical forces plays a part in the production of the condition described. The factors to be considered apart from this are anoxia, oedema, vascular disturbances, and fat embolism.

Anoxia.—There is no definite clinical evidence that these patients were anoxic shortly after the accident and before the neurological signs appeared, except Case 4 who began to have decerebrate attacks after severe respiratory obstruction due to inhaled vomit.

The pathological lesions which are usually ascribed to anoxia are strikingly absent in our cases. Classically anoxia affects nerve cells in the cerebral cortex, Ammon's horn, the globus pallidus and the Purkinje cells in the cerebellum (Hoff, Grenell, and Fulton, 1945; Heymans, 1950; Courville, 1953b), and such changes have been described in fatal head injuries by Malamud and Haymaker (1947). Such nerve cell damage is not present in our cases except in two instances. Case 5, a 73-year-old woman, had bilateral necrosis of Ammon's horn, but as an isolated finding this cannot be taken as evidence of generalized anoxia (Spielmeyer, 1925). Case 4 had an almost total loss of Purkinje cells in the cerebellum, without anoxic changes elsewhere. There was also a softening in one cerebellar lobe and the whole cerebellar lesion may have been due to local disturbances of the blood supply, though hypoxia may have contributed to this picture since the patient was very cyanosed on several occasions.

It is true that white matter degeneration due to anoxia does occur, especially under experimental conditions and when the anoxia is due to poisons (Hurst, 1942; Lumsden, 1950, chronic cyanide poisoning; Meyer, 1928b, chronic carbon monoxide poisoning). It has also been described in human carbon monoxide poisoning (Meyer, 1928a; Grinker, 1925; Strecker, Taft, and Willey, 1927) and after nitrous oxide anaesthesia (O'Brien and Steegmann, 1938; Courville, 1953a, Case 10) but such cases are rare and nearly always show the more typical changes of anoxia as well.

Anoxia is therefore not considered to have played a major part in the production of brain damage in the cases under discussion.

Oedema.—There can be no doubt that cerebral swelling due to oedema occurs in head injuries, nor that long-standing oedema can produce demyelination. The view that such a mechanism is important for the production of permanent brain damage after head injury has been put forward, notably by Evans and Scheinker (1944, 1945). None of our cases had clinical evidence of oedema, that is, there were no signs of raised intracranial pressure at any time and the lumbar or ventricular cerebrospinal fluid pressure when estimated during the first few days after the accident was within normal limits. It is difficult to believe that oedema severe enough to cause such extensive demyelination would have passed unnoticed clinically. The onset of decerebrate rigidity immediately after the injury (in Case 1 while still lying on the road) also makes oedema unlikely as the major factor.

The histology of the white matter in oedema as seen near tumours (Greenfield, 1939; Scholz, 1949), near abscesses, or after superior sagittal sinus thrombosis (Woolf, 1954) differs from that seen in our cases, particularly because fat granule cells are so few or absent in oedema.

It seems therefore that no good case can be made out for oedema as the cause for the white matter lesion.

Vascular Disturbances.—Lesions which are undoubtedly due to interruption of the blood supply

are seen in all the brains. They are the small haemorrhages and softenings, small cortical infarcts situated at the bottom of the sulci, and sclerosis of Ammon's horns in one case. These lesions are interesting but, it may be said at once, they are not sufficient to account for the degree of white matter change.

The question of the pathogenesis of these focal lesions must be left open at the moment. The view that they are due to a direct mechanical effect on blood vessels has been put forward by Bright (1831), Schmaus (1899), Jakob (1913), Denny-Brown and Russell (1941), and is favoured by the present author. Lindenberg (1955) has advanced the idea that they are due to compression of arteries by the swollen brain (or by pressure due to intracranial haematomata), but his arguments are not entirely convincing. There is also a school which believes that focal lesions and degenerative changes are due to malfunction of the vasomotor centre after concussion leading to stasis in the cerebral blood vessels with diapedesis of red cells or oedema and necrosis (Ricker, 1919; Marburg, 1936; Helfand, 1939; Courville, 1953a). Most of these authors base their arguments on the work of Ricker (1919). Ricker investigated the acute effect of trauma on blood vessels, using the rabbit's ear, mesentery, and pleura. He also studied the chronic effect of injury on the vascular system by observing the vessels of the pancreas after tying off its duct, and the effect of mesothorium irradiation on the vessels of the rabbit's ear. He then used the results of these investigations to infer what must be happening in the brain during, and in the weeks and months following, concussion. It is of great historical interest that he was able to do this without qualms, but such reasoning is no longer permissible.

There is no direct evidence that the focal or the diffuse lesions are due to vasomotor disturbances.

Fat Embolism.—There was no clinical evidence for this and the diffuse lesion is difficult to account for by such a mechanism. Fat embolism would be expected to produce focal areas of demyelination, such as have in fact been demonstrated experimentally by Woolf (1954).

Physical Injury.—The view that the degeneration of white matter is due to physical damage to nerve fibres at the time of the injury cannot be proved at present, but there is circumstantial evidence in its favour.

(1) Physical damage to the nervous system would account for the presence of permanent abnormal neurological signs so soon after the injury. (In the case of which there is an eye witness account, the signs were present within minutes if not seconds of the accident.)

(2) The histological picture is compatible with injury to nerve fibres severe enough to cause their death and secondary degeneration. The microscopic appearance of the diffuse white matter lesion is indistinguishable from that of known Wallerian degeneration in the same brain, *e.g.*, distal to a haemorrhage or in the descending tracts in the brain-stem and spinal cord.

(3) The complete sparing of whole or parts of some convolutions in areas where the degeneration is otherwise severe, and the markedly unequal degree of degeneration in the two pyramidal tracts in the presence of bilateral hemisphere damage suggest a mechanical cause for the lesion and are difficult to account for on any other basis. It is unlikely that oedema or anoxia can affect fibres so selectively.

(4) Stretching and tearing of nerve fibres and blood vessels throughout the brain is a likely consequence of head injuries accompanied by rotation, which produces shearing strains and distortion of the brain (Holbourn, 1943, 1945). The exact injury will depend on " the degree of distortion, on the nature of the distorted region and on the directions of the shear strains relative to fibre-directions " (Holbourn, 1945). These factors may account for widespread damage with sparing of some regions or some fibre tracts of the brain.

Some asymmetry such as the unilateral pyramidal tract degeneration is not unexpected (Holbourn, 1943, and personal communication) when the brain is rotated in a plane of symmetry, *e.g.*, the coronal or the horizontal plane. This is due to the fact that the two hemispheres are mirror images of each other. When the brain rotates so that, say, one temporal lobe moves downwards, the other temporal lobe will move upwards; corresponding damage in the two hemispheres would only be expected if both temporal lobes moved downwards.

Some of the lesions seen in the brains under discussion are almost certainly due to physical injury, for example the haemorrhages in the corpus callosum and the softening in the superior cerebellar peduncles.

Details of the accidents are not known, but the external marks of violence and the lateralization of the lesions are shown in Table II. The number of cases is too small and the information too scanty to draw any conclusions.

It is difficult to account for the degeneration of the tracts, other than the long descending tracts, in midbrain and pons, which is seen in all the cases, but it seems possible that this also is due to

disruption of nerve fibres at the time of the accident.

Thus there is much evidence in favour of mechanical damage as the chief cause for the lesions, though it is not conclusive.

Clinico-pathological Correlation

The most striking clinical features of our patients were the quadriparesis, usually spastic, and the grossly abnormal mental state. The patient in whom speech could be assessed was also aphasic. The mental state was characterized by an extreme indifference to the enviroment and by unresponsiveness except to crude stimuli. It may be tempting to refer to a patient in this condition as unconscious or comatose, but it is more correct that such patients should be called demented.

It is important to distinguish between these states if attempts at correlating the clinical picture with anatomical lesions are to be made, particularly perhaps to-day when much work is being done on defining the nervous centres necessary for the maintenance of consciousness.

The mental functions were not equally severely affected in all patients. One (Case 2) was able to ask and answer questions and recognized her relatives, two others (Cases 3 and 5) spoke a few words and obeyed simple commands. These three patients must have been conscious or aware of something in their environment. Two others (Cases 1 and 4) never spoke or obeyed commands, though apart from this their reactions did not differ from those of the first three patients. Patients 1 and 4 were so inaccessible that it is impossible to know whether they were conscious or not, but they (and the others) differ from comatose patients in several important respects.

Once the acute effect of the head injury had worn off, there was a clear difference between the waking and the sleeping state. They lay with their eyes open, looking round, for many hours at a time, even when not being stimulated.

They not only swallowed but chewed and were able to eat and drink though they could not feed themselves.

They blinked in response to menace. This reflex is one of the first to be lost when a patient is made unconscious by an anaesthetist.

They looked alert.

It would seem therefore that the two patients who did not respond to the spoken word were not more comatose than the three who did, but were even more demented.

Histological examination of the brain showed a severe diffuse degeneration of the white matter in the cerebral hemispheres, which had interrupted connexions between different areas of cortex, and between the cortex and the lower centres, and had produced secondary atrophy of large parts of the thalamus. Such a lesion can account for a severe generalized loss of cerebral function such as was shown by our patients. The lesion is severest in the patients who were most demented, in whom most of the anterior three-quarters of the brain were affected. The temporal and occipital regions were the least affected in all cases. In addition to the hemisphere lesion there was degeneration in the sensory tracts, that is, in one or both medial lemnisci in all cases, and in the lateral lemnisci or visual pathways in some, and this no doubt added to the indifference of the patients to sensory stimulation.

The white matter degeneration presumably also accounts for the quadriparesis seen in each patient. It is interesting that there was paralysis and spasticity bilaterally, although the degeneration in the two pyramidal tracts was markedly unequal in four cases. There was no correlation between the degree of paralysis or spasticity and the degree of pyramidal tract degeneration. That there is this lack of correlation is well known, and the literature on this point has recently been reviewed by Lassek (1950).

Only two of the four patients with unequal pyramidal tract degeneration lay in a strikingly asymmetrical posture (Fig. 18). In both, the side held in the so-called decerebrate position was innervated by the almost normal pyramidal tract.

So-called " brain-stem attacks " were observed in three patients and in Rosenblath's (1899) case. During these the patient assumes the decerebrate posture (Fig. 29) and there is profuse sweating and a rise in blood pressure and respiratory rate. Nothing can be said about the lesions responsible for these attacks except that they need not be evidence of midbrain haemorrhages.

Many features remain unexplained, among them are the non-neurological abnormalities which include the development of calcification of muscles in three out of five patients, the severe wasting in spite of an adequate diet in one, the complete absence of menstruation and the absence of growth of the hair for many months in another.

It will be apparent that the neurological abnormalities were severe and complicated and that the lesion and its secondary effects were so widespread that a detailed analysis is difficult, if not impossible.

Historical Survey of Studies of the White Matter in Head Injuries

One hundred years ago it was clear to all workers that, as Gama (1835) for instance put it, " fibres as delicate as those of which the organ of mind is composed are liable to break " as a result of violence

to the head. But in recent years little attention has been paid to the white matter in head injuries. This is partly because human pathological material from patients who survive an injury long enough for histological changes to develop is not readily available to neuropathologists, and also because slight or scanty changes are very difficult to see in the brain. Another reason is that experimenters have been mainly interested in concussion which is supposed to be either fatal or reversible, and not in mechanisms of brain injury which may leave neurological sequelae. Few head injury experiments with survival, which would be suitable to reveal damage to nervous tissue, are therefore on record.

One of the first long-term experiments was done by Witkowski in 1877. Amongst other animals he used frogs which he stunned by hitting their heads against a table. After a few times this produced permanent changes such as unsteadiness, weakness, and lack of will power, a picture apparently reminiscent of human patients with general paralysis. Microscopical examination showed petechial haemorrhages in the brain substance, but staining methods were not then generally available.

Schmaus (1890, 1899) studied spinal cord concussion in rabbits produced by blunt injuries to the back. He found secondary degeneration of nerve fibres above and below the level of injury without obvious focal damage. This was later confirmed by Jakob (1913). Schmaus came to the conclusion that the nerve fibres died as a result of mechanical damage.

An important study was published by Jakob in 1913, who concussed rabbits and monkeys by letting a hammer of known weight fall on their heads from a known height. This procedure was repeated, sometimes on successive days, until permanent signs appeared such as clumsiness, nervousness, and loss of appetite. At necropsy diffuse degeneration of the white matter, which could not be accounted for by focal lesions, was found in the brains of all the animals which survived the injury for long enough to show up the lesion (two days). Degeneration was found in the cerebral hemispheres, in descending and ascending tracts in the brain-stem, in the cerebellum, and around the margin of the pons and medulla. The changes were best seen in Marchi preparations and showed the histological characteristics of secondary degeneration. It was pointed out, however, that the cellular reaction was considerably slower than that in secondary degeneration after section of the spinal cord or decortication.

Jakob's experimental findings are very similar to ours in human material. He considered that primary traumatic damage, which could be either reversible or lead to necrosis of the nerve fibres, was the basis for his findings and that circulatory disturbances did not play a part.

Careful long-term experiments were carried out by Windle, Groat, and Fox (1944) and by Groat and Simmons (1950) on guinea-pigs. These authors reported changes in nerve cell bodies but did not find significant abnormalities in the nerve fibres. They did not use the Marchi technique, however, without which slight damage would be very difficult to see.

Amongst workers interested in the physical aspects of the problem of head injury, Gama (1835) was probably the first to make use of brain models for experiments. He filled glass flasks with jelly in which he embedded black threads. When a flask was struck he observed a to-and-fro movement of the threads. Gama concluded that concussion was due to vibration (*ébranlement*) of the brain. These ideas were attacked first by Alquié (1865) and later by Fischer (1871). Both these workers repeated and extended Gama's experiments but failed to confirm his observations. If there is all this vibration, Fischer asked, why is there no tearing of the nerve fibres? But he never investigated this point. Both Fischer and Alquié thought that there was mass movement of the brain away from the point of impact, though Fischer did not think that concussion was due to this but to sudden anaemia of the brain.

In an attempt to prove that concussion was due to a sudden increase in intracranial hydrostatic pressure, Ferrari (1882) experimented with skulls filled with brain tissue or gelatin, in which he implanted microscope cover slips or glass capillary tubes. He then allowed a heavy iron ball to fall from various heights on to the skull which was firmly held or tied down. In many experiments the skull was shattered, but even when it was not, the cover slips, but not the capillary tubes, broke as long as they were implanted not more than 0·5 cm. away from the skull. In these experiments the mechanism is analogous to that in "compression concussion" (Denny-Brown and Russell, 1941), whereas our cases suffered from "acceleration concussion" since the head was almost certainly free to move after the blow.

The work of Holbourn (1943, 1945), who approached the subject from a physicist's point of view, has already been mentioned. He considered that of all the forces acting on the head during a blow, rotational acceleration forces and the accompanying shear strains would be the most injurious to a body with the physical properties of brain, that is one that is very incompressible but easily distorted. He constructed a gelatin brain

model which he subjected to rotation in a circular polariscope, thus rendering the shear strains visible. He thought that these forces would be sufficient to disrupt nerve fibres, blood vessels, synapses, and so on. Since the brain is enclosed in a rigid skull, the only way it can react to forces which tend to distort it is by gliding and swirling movements.

Pudenz and Shelden (1946) recorded the movement of the brain during a blow to the head by high-speed cinematography, using monkeys whose skull caps had been replaced by transparent material. They found gliding and swirling movements of the brain even after subconcussive blows if the head was free to move. When the head was fixed, movements of the brain were much reduced or absent.

White matter lesions in human cases of head injury have only occasionally been described. In 1899 Rosenblath reported the case of a 16-year-old tight-rope walker who fell and was immediately rendered unconscious. Most of the time he lay motionless in what is described as a sleep-like state. He had attacks of decerebration and became very spastic, with one arm extended, the other flexed. He required full nursing care including tube feeding and died eight months after the accident. At necropsy there were no fractures of the skull. The brain weighed only 930 g.; there was ventricular dilatation. There was an immense loss of nerve fibres throughout the cerebral hemispheres and there were a few small softenings, including one in the corpus callosum and one in the superior cerebellar peduncle. Degeneration could be traced into the cortex (in this respect the case differs from ours) but there was no cell loss. There was degeneration in the occipital radiation, in the descending tracts, in the lateral and medial lemnisci from the middle of the pons upwards, and in the white matter of the cerebellum. The resemblance to our cases is very striking. Rosenblath considered that the nerve fibre loss was due to the effect of the concussion itself on the fibres.

In 1904 Meyer reported the case of a boy whose gun exploded, injuring the left frontal lobe. The patient was soon so well that no neurological examination was made, but he died unexpectedly four weeks after the injury and at necropsy pus was found in the ventricles of the brain. Marchi preparations of the brain showed that apart from degeneration due to the destruction of the frontal lobe there was slight but unmistakable degeneration in the internal capsule, even in the posterior limb, in the external capsule, in the pyramids, in the medial and lateral lemnisci, and a superior cerebellar peduncle. Meyer concluded that the effects of the concussion had been very widespread in this case.

Both Russell (1932) and Greenfield (1938) discussed and stressed the probable importance in concussion of interruption of function of nerve fibres and their sheaths by mechanical damage.

In their studies on nerve fibres in head injury, Rand and Courville (1934) found retraction bulbs in the neighbourhood of haemorrhages and underneath cortical contusions. They also mention that retraction bulbs are occasionally seen in areas remote from any focal lesion.

Evans and Scheinker have been interested in the white matter in head injuries and in 1944 reported several cases with lesions from a few days to many years old, in which there was marked fibrous gliosis and sometimes demyelination of the centrum semiovale with a normal cerebral cortex. This they thought was due to prolonged hypoxia and oedema of the brain due to circulatory disturbances following the injury.

CONCLUSION

It has been shown that a closed, apparently uncomplicated head injury may be followed by a diffuse degeneration of the white matter and consequently may completely and permanently incapacitate the patient. The extreme dementia produced by such a lesion should not be confused with coma, which has different physical signs. The nerve fibre degeneration is not due to cortical cell loss, nor to infarction or laceration of brain substance. Its pathogenesis has not been determined but evidence points to physical damage of nerve fibres at the time of injury as a likely cause.

It is at present not possible to say how frequently such white matter degeneration occurs because it has not been looked for in acute head injuries. In our series of 26 patients dying from head injuries six weeks or more after the accident, it was the significant pathological finding in about one-third of the cases.

It is impossible to say whether the nerve fibre damage is at any time reversible and what part, if any, it plays in the production of the signs of concussion, but the possibility that it may play a part should be borne in mind.

It should be remembered that such a diffuse white matter lesion may have to be looked for with care and that it is not enough to examine the brain-stem reticular formation or the cerebral cortex when investigating cases of severe disturbance of consciousness after head injury.

I am grateful to Dr. P. M. Daniel for his invaluable advice, criticism, and enthusiasm at all stages of the work. I am indebted to Dr. P. Glees for sections of the basal ganglia of Case 2. My thanks are due to Dr. M. M. L. Prichard and Mr. E. L. Tugwell for the photographs,

and to Mr. R. Beesley and Miss E. Stanley for technical assistance. I am grateful to Mr. W. S. Lewin for permission to use the clinical notes of the patients under his care. This work was done while in receipt of a personal grant from the Medical Research Council.

REFERENCES

Alquié, A. (1865). *Gaz. méd. Paris*, 3 ser., **20**, 226.

Bright, R. (1831). *Reports of Medical Cases*, vol. 2, pt. 2, p. 681. Longman, Rees, Orme, Brown, and Green, London.

Courville, C. B. (1953*a*). *Commotio Cerebri*. San Lucas Press, Los Angeles.

—, (1953*b*). *Contributions to the Study of Cerebral Anoxia*. San Lucas Press, Los Angeles.

Denny-Brown, D., and Russell, W. R. (1941). *Brain*, **64**, 93.

Evans, J. P., and Scheinker, I. M. (1944). *J. Neurosurg.*, **1**, 306.

—, —, (1945). *Res. Publ. Ass. nerv. ment. Dis.* **24**, 254.

Ferrari, A. (1882). *Spallanzani* (Modena) 2nd ser., **11**, 169.

Fischer, H. (1871). In *Sammlung klinischer Vorträge*, ed. R. Volkmann. *Chirurgie*, **1**, No. 8, p. 119. Breitkopf and Härtel, Leipzig.

Gama, J.-P. (1835). *Traité des Plaies de Tête et de l'Encéphalite*, Crochard, Paris.

Glees, P. (1943). *Brain*, **66**, 229.

Greenfield, J. G. (1938). *Proc. roy. Soc. Med.*, **32**, 43.

—, (1939). *Brain*, **62**, 129.

Grinker, R. R. (1925). *Z. ges. Neurol. Psychiat.*, **98**, 433.

Groat, R. A., and Simmons, J. Q. (1950). *J. Neuropath.*, **9**, 150.

Helfand, M. (1939). *J. nerv. ment. Dis.*, **90**, 157.

Heymans, C. (1950). *Physiol. Rev.*, **30**, 375.

Hoff, E. C., Grenell, R. G., and Fulton, J. F. (1945). *Medicine* (*Baltimore*), **24**, 161.

Holbourn, A. H. S. (1943). *Lancet*, **2**, 438.

——, (1945). *Brit. med. Bull.*, **3**, 147.

Hurst, E. W. (1942). *Aust. J. exp. Biol. med. Sci.*, **20**, 297.

Jakob, A. (1913). In *Histologische und histopathologische Arbeiten, über die Grosshirnrinde*, Vol. 5, p. 182. Ed. Nissl, F., and Alzheimer, A. Fischer, Jena.

Lassek, A. M. (1950). *Brain*, **73**, 95.

Lindenberg, R. (1955). *J. Neuropath.*, **14**, 223.

Lumsden, C. E. (1950). *Journal of Neurology, Neurosurgery and Psychiatry*, **13**, 1.

Malamud, N., and Haymaker, W. (1947). *J. Neuropath.*, **6**, 217.

Marburg, O. (1936). In *Handbuch der Neurologie*, ed. Bumke, O., and Foerster, O., vol. 11, 1. Springer, Berlin.

Meyer, A. (1904). *Amer. J. Insan.*, **60**, 373.

Meyer, A. (1928*a*). *Z. ges. Neurol. Psychiat.*, **112**, 172.

——, (1928*b*). *Ibid.*, **112**, 187.

O'Brien, J. D., and Steegmann, A. T. (1938). *Ann. Surg.*, **107**, 486.

Pudenz, R. H., and Shelden, C. H. (1946). *J. Neurosurg.*, **3**, 487.

Rand, C. W., and Courville, C. B. (1934). *Arch. Neurol. Psychiat.* (*Chicago*), **31**, 527.

Ricker, G. (1919). *Virchows Arch. path. Anat.*, **226**, 180.

Rosenblath, W. (1899). *Dtsch. Arch. klin. Med.*, **64**, 406.

Russell, W. R. (1932). *Brain*, **55**, 549.

Schmaus, H. (1890). *Virchows Arch. path. Anat.*, **122**, 326, 470.

——, (1899). *Münch. med. Wschr.*, **46**, 75.

Scholz, W. (1949). *Arch. Psychiat. Nervenkr.*, **181**, 621.

Smith, M. C. (1956). *Journal of Neurology, Neurosurgery and Psychiatry*, **19**, 67.

——, Strich, S. J., and Sharp, P. (1956). *Ibid.*, **19**, 62.

Spielmeyer, W. (1925). *Z. ges. Neurol. Psychiat.*, **99**, 756.

Strecker, E. A., Taft, A. E., and Willey, G. F. (1927). *Arch. Neurol. Psychiat.* (*Chicago*), **17**, 552.

Windle, W. F., Groat, R. A., and Fox, C. A. (1944). *Surg. Gynec. Obstet.*, **79**, 561.

Witkowski, L. (1877). *Virchows Arch. path Anat.*, **69**, 498.

Woolf, A. L. (1954). *J. Path. Bact.*, **67**, 1.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 186.

RETINAL DEGENERATION IN HEREDITARY ATAXIA

BY

Å. BJÖRK, U. LINDBLOM, and L. WADENSTEN

From the Eye Clinic, Karolinska Hospital, and the Neurological Clinic, Serafimerlasarettet, Stockholm

Deterioration of vision is a not infrequent occurrence in cases of hereditary ataxia. Like the ataxic symptoms it is progressive and may become severe. According to the literature the deterioration of vision has been ascribed to optic atrophy in the majority of cases and only in a few instances are retinal changes or cataract described. It is obvious, however, that the actual findings have often been very slight and that in some cases the ophthalmoscopical picture has been recorded as normal despite a strong reduction in visual acuity (Bell and Carmichael, 1939; van Bogaert, 1948).

The present study gives an account of five cases of hereditary ataxia associated with serious loss of vision. The patients have been subjected to careful examination including electroretinography(E.R.G.) in four of the cases. This examination has revealed new facts that elucidate the problems associated with the causation and progression of impairment of vision in this disorder.

Methods

Each patient was subjected to exhaustive neurological and ophthalmological examination. The visual fields were generally studied in a perimeter of hemispherical form (model Haag and Streit) with a circular white test object of 0·5 cm. in diameter. The light sense was tested by determining the minimum perceptible after 30 minutes of dark adaptation using Carle's modification of the Gullstrand photometer. The colour sense was investigated by means of pseudo-isochromatic tables and the Nagel anomaloscope.

The E.R.G. was recorded by Karpe's (1945, 1948) technique, with a contact glass filled with physiological saline covering the corneal surface as the active electrode, a second electrode being attached to the forehead. The potentials were fed to a condenser-coupled amplifier and the records were made on moving paper film by means of two oscillographs, one for the actual E.R.G. and the other for the light stimulus. When single-flash E.R.G. was to be studied the stimulus consisted of a short flash of " white light " of about $\frac{1}{17}$ second duration. Three light intensities were used: 20, 80, and 800 lux when measured at the plane of the eye. In flicker E.R.G. the

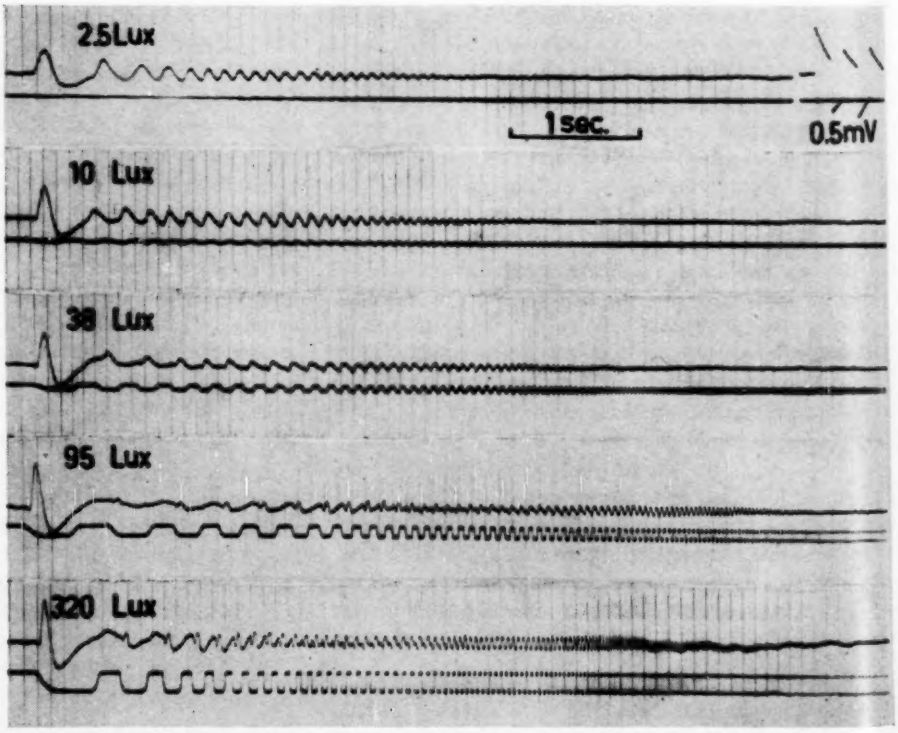


FIG. 1.—Flicker E.R.G. from standard case. Flicker of scotopic type at low illumination intensities, of photopic type at high intensities. Flicker fusion frequency increasing from 15 per sec. at low lux values to about 70 at maximum illumination.

technique described by Dodt and Wadensten (1954) was used. The stimulus was produced by hand rotation of a sectored disc which interrupted a maintained light. Each period of illumination was followed by an equally long period of darkness. The flicker was varied with respect to frequency as well as to intensity of illumination, the latter varying from 1 to 400 lux.

Single-flash E.R.G. in man, as recorded according to Karpe, normally shows a high positive potential (b-potential) of a mean amplitude of 0·34 mV, sigma being 0·06 mV. In the following cases the mean amplitude has been statistically classified as follows:

$m \pm 3\sigma$ is almost certainly abnormal outside the limits (below $m - 3\sigma$ is a " subnormal " E.R.G.).

$m \pm 2{\cdot}5\sigma$ is very probably abnormal outside the limits.

$m \pm 2\sigma$ is probably abnormal outside the limits.

A relationship between the magnitude of the b-potential and the activity of the rod system has been established by experiments on animals and clinical investigations (*cf.*, Granit, 1947; Karpe, 1945; Karpe and Tansley, 1948).

In interpreting the flicker E.R.G. special attention is given to the flicker fusion frequency (F.F.F.) and to the shape of the flicker waves. Flicker fusion frequency has been defined as the highest stimulus frequency at which every flash is still accompanied by a wave, and it is generally seen that the higher the F.F.F. the stronger the stimulant illumination used. Fig. 1 shows how the normal flicker E.R.G. changes with increasing stimulus intensity. At low intensities there are small rounded b-waves and the F.F.F. does not exceed 25 per second (scotopic flicker). At higher intensities the b-waves are more pointed and are interspersed with small negative a-waves, and the F.F.F. is high, up to about 70 per second (photopic flicker).

Experiments on animals have shown that the scotopic flicker is related to the rod function and the photopic flicker to the cone function of the retina (*cf.* Granit, 1947). In accordance with this it has been found that cases of total colour blindness produce a flicker E.R.G. of purely scotopic type (Dodt and Wadensten, 1954; Wadensten, 1954, 1956).

It may be of value to point out here that neither single-flash E.R.G.s nor flicker E.R.G.s are influenced by lesions concerned with the visual paths only, *e.g.*, a descending optic atrophy; but that they only reflect retinal changes. Furthermore, only extensive retinal lesions seem to influence the E.R.G. Hence neither isolated macular lesions nor limited retinal lesions of other types cause changes in the E.R.G. (Karpe, 1945, 1955; Wadensten, 1956).

Case Reports

Case 1.—A Hj-m, a woman, born in 1939 (No. 140/55), had healthy maternal grandparents, and no nervous disease was known among relatives except in the case of the mother, who was treated in 1938 (No. 519/38) in the Neurological Clinic for syndroma cerebellare progressivum and atrophia retinae.

When examined in 1938 her mother was 21 years old and her ophthalmological state was described thus: " Visual acuity 0·1 in both eyes; visual fields for white normal; total colour blindness; fundi, a manifest retinal atrophy affecting both eyes and especially clearly seen in the pigment layer. Blood vessels very narrow. Moderate atrophy of papillae, probably secondary to the retinal changes. Maculae show the same changes as other parts of the fundi and, further, creased macular reflexes as after a macular oedema." Deterioration of vision had been noticeable at the age of 10, and since the age of 14 or 15 she had experienced difficulty in keeping her balance and during the last year her gait had been unsteady.

At a neurological examination of Case 1 in 1955 the gait was jerky, with side-stepping and a positive Romberg's sign. Diadochokinesis was impaired on both sides. In the finger-nose and knee-heel tests a slight trembling occurred towards the end of the movement, but this was not necessarily pathological. Muscular reflexes generally were lively, particularly in the legs. Babinski's sign was negative on both sides. Sensibility, gross power, and cranial nerves seemed to be normal; caloric nystagmus movements were slower than normal. *X*-ray examination of the skull was normal, and the E.E.G. showed moderate non-specific abnormality without any definite localization. Her psychic state was normal. The internal organs were normal, there was no endocrine disorder. Blood tests for syphilis were negative.

At an ophthalmological examination in 1949 the visual acuity was 0·5 for each eye. It has diminished gradually since then, values being 0·3 for each eye in 1950, and 0·2 (right) and 0·1 (left) in 1951. In 1952 an examination showed 0·1 on each eye, a value that has since then remained almost unchanged. There was no refraction anomaly of importance.

Starting in 1951, exhaustive examinations, including E.R.G., were performed almost every year. At the beginning the ophthalmoscopical examination showed the fundi to be quite normal. At the examination in 1953 the vessels were somewhat narrow, and the structure of the retina seemed to be slightly granular. These findings were more distinct at the most recent examination (1955). There seemed to be an increase in pigmentation both peripherally and within the maculae.

The visual fields for white showed normal limits in 1953 but in 1955 there was a moderate narrowing of the fields in both eyes. The light sense, last tested in 1954, showed nothing definitely abnormal. The colour sense as tested with pseudo-isochromatic plates was already defective in 1951. Anomaloscope examination in 1953 resulted in equations suggesting total colour blindness.

A single-flash E.R.G. was recorded on four occasions. The following table shows the amplitudes of the b-potential as recorded in the different examinations (mean values) :

1951 (right) 0·32 mV (left) 0·35 mV
1953 (right) 0·33 mV (left) 0·28 mV
1954 (right) 0·27 mV (left) 0·26 mV (see Fig. 2)
1955 (right) 0·23 mV (left) 0·21 mV

The intensity of the illumination was 20 lux in each case.

Although all values are probably normal the continuous decrease in amplitude is striking.

In the last three examinations, flicker E.R.G.s were included. Already in 1953 the flicker E.R.G. disclosed

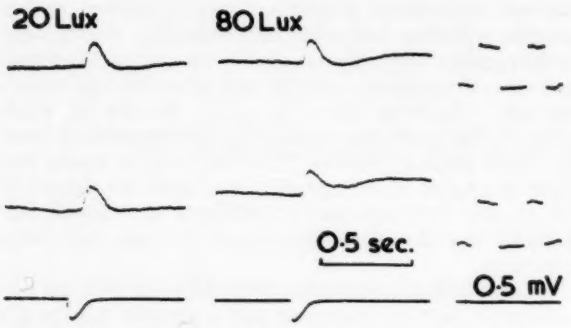


FIG. 2.—Case 1 (1954). Single flash E.R.G. from right (upper curve) and left eye (middle curve) at 20 and 80 lux. Flash recorded by lower curve. Amplitudes of b-waves at 20 lux are 0·27 mV (right) and 0·26 mV (left eye); almost unchanged at 80 lux. Values within normal limits.

signs of impaired cone function. The 1954 investigation showed that there was pronounced disturbance of the cone function since only a scotopic response could be obtained even at strong intensities of illumination (Fig. 3). The flicker E.R.G. examination in 1955 showed substantially the same picture as in 1954.

The visual disturbances in this case, which constituted the only symptom for some years, could not be explained by routine eye examinations. No objective findings could be made apart from the initially very vague fundus findings. Owing to this uncertainty, highly varying conclusions were arrived at on different occasions, such as suspected aggravation or hysteria, or, later on, the diagnosis of juvenile degeneration of the macula. Although the falling values of the b-potential in single-flash E.R.G. would suggest a progressive lesion to the retinal function, nothing could be said with certainty since the values obtained were not actually pathological. Only the flicker E.R.G. proved the existence of a wide-spread pathological process in the retina, involving the cone function. Later on ataxic symptoms appeared thus establishing the diagnosis of hereditary ataxia. There is reason to believe that at a still later stage the patient will develop distinct ophthalmoscopic changes in the retinae, possibly of the same type as had been observed in her mother.

Case 2.—M. H-n, a woman, was born in 1936 (Nos. 254/51 and 145/55). The patient's mother and maternal uncle, as well as her maternal grandmother and two siblings of the maternal grandmother, suffered from hereditary ataxia.

The patient herself had suffered from impaired visual acuity from the age of 7, and her illness had gradually become worse during the last years. She now saw best in dim light. From the age of 17, the patient had experienced difficulty in keeping her balance, and her gait was gradually becoming more unsteady.

A neurological examination in 1951, including pneumoencephalography, showed no abnormality. In 1955

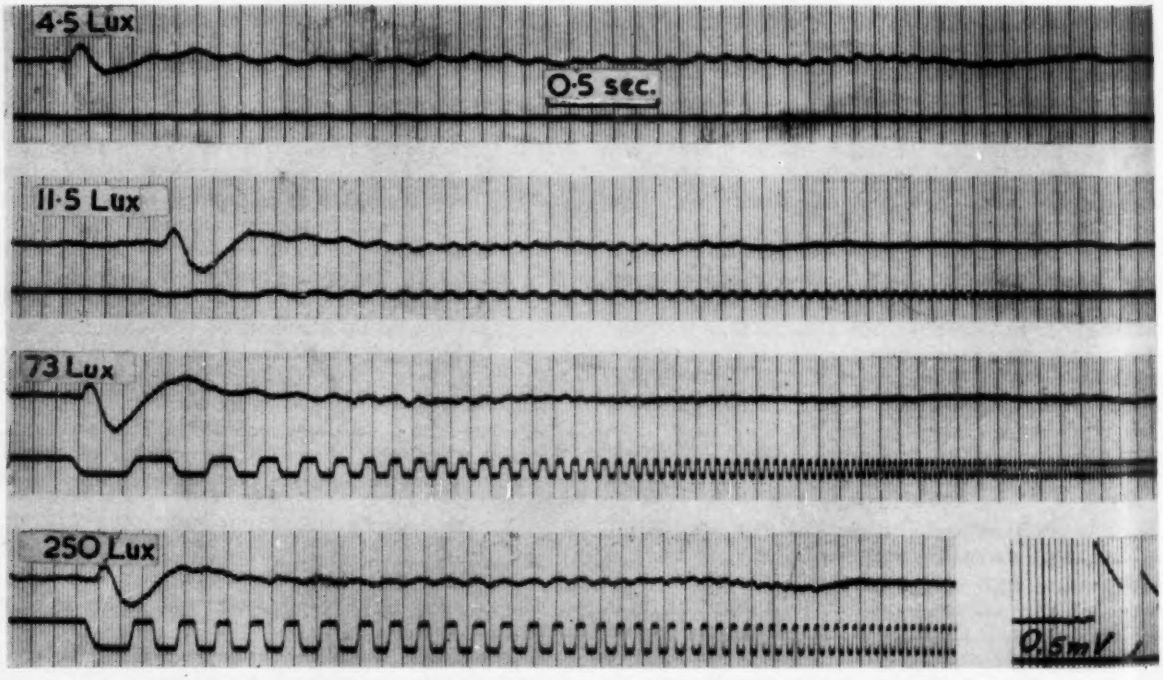


FIG. 3.—Case 1 (1954). Flicker E.R.G. at various intensities of stimulus illumination. Curves recorded simultaneously with curves in Fig. 2. All curves show scotopic flicker without signs of photopic potentials. Flicker fusion frequency about 15 per sec. at 4·5 lux, about 20 per sec. at stronger intensities.

examination revealed a slight deviation of gait to the right or left and a positive Romberg's sign. Diadochokinesis was impaired on both sides and there was slight dysmetria when trying to write. In the knee-heel test a slight tremor occurred on both sides. All muscular reflexes were lively, particularly in the legs, though not definitely increased and Babinski's sign was negative on both sides. Sensibility, gross power, and cranial nerves were normal. A caloric test resulted in slower nystagmus movements than usual. A radiograph of the skull and an E.E.G. revealed nothing abnormal. Her psychic state was normal. The internal organs were normal. She had no endocrine disorders, and tests on blood and cerebrospinal fluid for syphilis were negative.

In 1948, when the patient was 12 years old, an ophthalmological examination revealed a visual acuity of 0·5 for each eye; in 1951 the corresponding values were 0·1 to 0·2 (right eye) and 0·1 (left eye). The loss of visual acuity had become more severe during recent years, and at the last examination (1955) the values were just below 0·1 for each eye. On no occasion had it been possible to improve the conditions by using correcting glasses.

Examinations of the fundi in 1948 and 1951 showed nothing definitely pathological, but in 1954 and 1955 the papillae were of a yellowish pallor, and the vessels were narrow, in some places very narrow. Within the macula areas the pigment was perhaps somewhat agglomerated.

The limits of the visual fields for white were almost normal all the time. The light sense showed moderately pathological conditions. In 1954, the minimum perceptible was about 40/100·000 lux and, in 1955, about 100/100·000 lux. The colour sense proved to be seriously defective at the anomaloscopic examination in 1954, the values being almost identical with those found in total colour blindness.

The following table shows the amplitude of the b-potential at a stimulant illumination of 80 lux in single flash E.R.G. (mean values) :

1951 (right) 0·29 mV (left) 0·33 mV
1954 (right) 0·17 mV (left) 0·18 mV
1955 (right) 0·13 mV (left) 0·16 mV (see Fig. 4)

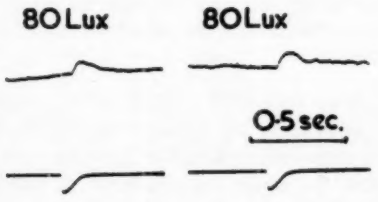


FIG. 4.—Case 2 (1955). Single flash E.R.G. of right and left eye. Calibration as in Fig. 2. Amplitude of b-waves, about 0·13 mV (right) and 0·16 mV (left). Subnormal E.R.G.

Hence the values obtained in 1951 are normal, the 1954 values are very probably abnormal, and those from 1955 are subnormal.

Flicker E.R.G.s were performed on two occasions, namely, in 1954 and 1955. Both times the curves were clearly pathological, the response being entirely scotopic even at high illumination intensities.

There is a definite resemblance in the clinical picture of this patient and that of Case 1. In both cases the ataxic symptoms were preceded by lowered visual acuity, the cause of which long remained doubtful. Flicker E.R.G.s revealed pathological conditions indicating an impaired cone function at a stage when a single flash E.R.G. still showed marginal values. In this case, however, even single-flash E.R.G.s yielded pathological values at the latest examination which may be interpreted as a spreading of the retinal affection to involve the rod function as well.

Case 3.—M. G. T-s, a woman, was born in 1936 (No. 630/54). The patient's family was explored over five generations. In all, 29 male and female members of this family, not counting the patient herself, had shown a clinical picture resembling that of the patient. She had inherited the disease through her mother (Case 5) and maternal grandmother, who were both affected. The maternal grandparents were first cousins. Some cases in another branch of the same family were investigated by Sjogren (1943, family 72).

From the age of about 11 the patient had experienced difficulty in keeping her balance and in speaking. Her balance had gradually become worse. During the same period she had been suffering from a progressive deterioration of vision and difficulties in distinguishing colours.

The patient did not go to a doctor until 1954 when she was 18. On neurological examination the gait was jerky, with frequent and long sidesteps, and with Romberg's test the patient reeled but did not fall. She showed slight dysmetria when performing finger-nose and knee-heel tests. Her speech was somewhat scanning. She had no aphasia. The muscular reflexes were very lively, especially in the legs, but not clearly increased. The Babinski sign was negative bilaterally. Sensibility, gross power, and cranial nerves were normal. An E.E.G. showed moderate generalized episodic abnormality. Her psychic state was normal. The internal organs were normal and there were no endocrine disturbances. Blood tests for syphilis were negative.

At an ophthalmological examination in 1954 visual acuity was scarcely 0·2 for each eye (with + 1·5 cyl. 90°) and corneal astigmatism (as determined in the Javal-Schiotz ophthalmometer) was + 3·0 D. 90°.

Fundi showed somewhat narrow arteries and a slight though coarsely granulated pigmentation of the maculae. The same type of possibly pathological pigmentation was also seen in the periphery.

The visual field for white showed normal limits. The light-sense values were pathological, though only slightly, minimum perceptible being about 20/100·00 lux. This figure, however, is rather uncertain, owing to the patient's being disturbed by subjective light phenomena. Though highly defective, the colour sense had not deteriorated to the degree described in Cases 1 and 2, but was of the same type.

The single-flash E.R.G. (Fig. 5) was subnormal. The potential of the right eye was 0·12 mV and of the left eye 0·10 mV at an illumination of 80 lux. Somewhat lower values were obtained when using 20 lux: right eye, 0·09 mV, left, 0·08 mV. With 800 lux the deflection was very small: the b-potential was scarcely measurable and was preceded by a distinctly negative wave.

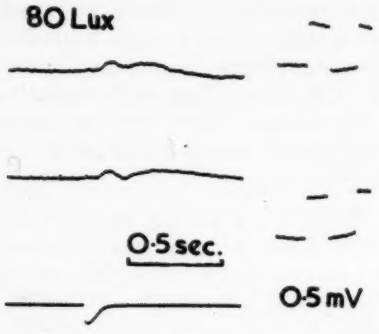


FIG. 5.—Case 3. E.R.G. of right and left eye. Amplitudes of b-waves, about 0·12 mV and 0·10 mV, respectively. Subnormal E.R.G.

The flicker E.R.G. was mainly of the scotopic type but included scattered a-waves when the illumination was 300 lux or more. Flicker fusion frequency did not exceed 45 per second.

This patient did not present herself for examination until seven years after the onset of symptoms. The ophthalmoscopical picture indicated a retinal affection, most probably a macular degeneration. Single-flash E.R.G. indicated a widespread, severe functional lesion involving the rod function. Flicker E.R.G. showed the cone function to be also damaged, though less severely than in the two preceding cases, which is further consistent with the fact that both the colour sense and the visual acuity were a little better in the present case.

Case 4.—T. G., a man, was born in 1917 (Nos. 401/51 and 17/56). The patient's maternal grandmother, mother, a maternal aunt, two maternal uncles, and two first cousins were similarly affected.

At the age of 10 he had been forced to discontinue balancing exercises at school but had otherwise been in good health until about the age of 25, when he had noticed difficulty in walking and diminution of visual acuity. The symptoms had steadily progressed and by the age of 31 he had been compelled to give up his job as a machine fitter.

Neurological examinations were made repeatedly during the years 1943 to 1951. Examination in 1943 had revealed ataxic gait, incoordination of the arms and slight ataxia of the trunk. In 1951 he had, in addition, dysarthria and increased deep reflexes in both legs. A pneumoencephalogram at this time was essentially normal. Tests for syphilis on the blood and cerebrospinal fluid were negative.

A fresh neurological examination in 1956 showed that the symptoms were more pronounced. The patient's gait was ataxic and spastic and he was able to walk only with the support of two persons though gross power was good. The Babinski sign was bilaterally positive. His speech was slow, slurred, scanning, and nasal. The tongue moved slowly and tended to deviate towards the left. Changes in facial expression and eye movements were slow. No other abnormality of the cranial nerves was noted. The sensibility was normal. Skull radiographs and an E.E.G. were normal.

Mental status showed no definite abnormality. Examination of the heart, lungs, and abdomen revealed no abnormality apart from radiological evidence of residues from an earlier pulmonary tuberculosis. He had no endocrine disorder.

Ophthalmological examination was performed on four occasions. The visual acuity was as follows:—

1945	0·6	(right)	0·5	(left)
1948	0·3	,,	0·3	,,
1951	0·1	,,	0·2	,,
1956	+1/50	,,	+1/50	,,

Vision was not improved with glasses.

Ophthalmoscopical examination showed normal fundi up to 1951. Examination in 1956 showed slight destruction of the central part of the maculae with migration of the macular pigment towards the periphery and no foveal reflex. The fundi were otherwise normal. The papillae were of normal colour and no other evidence of pigment abnormality was seen.

The investigation in 1956 in addition showed moderate concentric restriction of the visual fields for white. Light sense: minimum perceptible 8-10/100·000 lux, thus almost normal. The colour sense was markedly abnormal. At anomaloscopic examination this case was not quite like the others. The range of adjustment was very large, more than 20 lines on the screw, and thus also differed from primary total colour blindness.

A single-flash E.R.G. showed that the mean amplitude of the b-potential was 0·20 mV with a stimulus of 80 lux. This is probably abnormal. A flicker E.R.G. was abnormal in both the right and the left eye: flicker fusion frequency did not exceed 55/sec. and was attained first with a stimulus of 700 lux. A light intensity of more than 200 lux resulted in a few small photopic potentials in the record.

In this case impaired visual acuity and ataxic symptoms appear to have occurred about the same time. The ophthalmoscopical picture was normal up till 1951 in spite of marked impairment of vision. Examination in 1956 showed moderate degeneration of the maculae. The E.R.G. revealed a widespread retinal degeneration. It is remarkable that the E.R.G. changes were actually not more pronounced than in Cases 1, 2, and 3, despite the fact that he was examined at a more advanced stage of the disease. This may possibly be explained by the fact that the maculae were more extensively involved in this case.

Case 5.—M. T-s, born in 1914, was the mother of Case 3.

The patient had begun to suffer from visual trouble and difficulties in keeping her balance about the age of 12. Symptoms had become progressively worse and the patient had been admitted to a home in 1950. Since 1952 she had been entirely bedridden.

The patient was examined in 1954. She was extremely emaciated. On physical examination the heart was normal. The patient could orientate herself in time and space but cooperated with the examiner only to the extent of answering " yes " and " no ". She was capable of repeating isolated numerals and words of moderate length but could not contribute to the case history by giving anamnestic information. She was scarcely capable of lifting her feet from the bed. She had contractures of the hip and knee joints. The gross power of the hands was satisfactory. Movement of the hands and arms was incoordinated. Muscular reflexes were lively. The Babinski sign was positive bilaterally. The patient noticed pricking by a needle and also when her hands or feet were touched, and was aware of gross movements of her toe and finger joints. Her speech was unmodulated, drawling, and difficult to apprehend. She was capable of noticing smell, could eat, swallow, and cough; her voice was hoarse. She could hear whispering at more than three metres bilaterally.

An ophthalmological examination in 1954 showed light perception with uncertain localization, equal on both sides. The media of the eyes were clear. Both fundi displayed a considerable atrophy of the choroid and retina. The pigment was very scarce and agglomerated to form a loose network in the periphery, and there were isolated pigmented clumps akin to retinitis pigmentosa. The white colour of the sclera and the substantially thrombosed and sclerosed choroidal vessels were the principal features. The atrophies were especially distinct around the periphery and within a central area almost coinciding with the macula which, consequently, gave the impression of being punched. The papillae were pale and greyish, vessels narrow though not filamentous (Fig. 6).

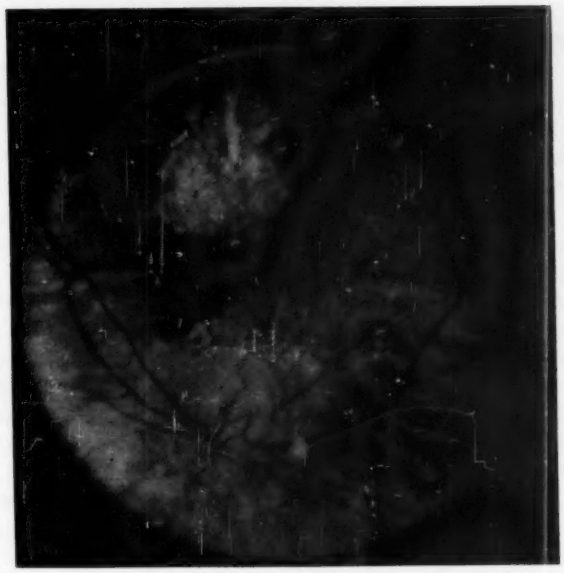


FIG. 6.—Case 5. Photograph of right fundus. The left fundus gave an identical picture.

Owing to the patient's bad general condition it was not possible to perform a complete ophthalmological investigation as in the preceding cases. However, Case 5 shows the advanced stage of retinal and choroidal atrophy, as illustrated in Fig. 6, to which the preceding cases may also be expected to proceed.

Discussion

The five cases reported here all showed distinct signs of ataxia, and it was possible to obtain reliable information on similar cases in the families concerned. The diagnosis of hereditary ataxia is believed to be accurate in each case. Although it does not seem necessary here further to classify the cases, all of them would fall under the category of hereditary ataxia of Pierre Marie's type.

The similarity in the symptoms and course of the disease in these five cases, although they belong to four different families, is one of their most striking features. They differ mainly in that they represent various stages. The examinations have revealed a widespread affection of the retina in each case and this is no doubt sufficient to account for the loss of vision. There seems to be no reason to presume the existence of lesions in the optic nerves or in more central parts of the visual pathways to explain the impairment of vision.

By means of E.R.G. it has been proved that the cases described here belong to a fairly well-defined and characteristic type of widespread progressive retinal degeneration. Both the cone and the rod systems are involved, though to a certain extent selectively, and it is suggested that the development of the disease is as follows. First, there is a disturbance of the cone function with progressive defect of colour vision and visual acuity, while the rod function remains relatively intact. Later, the rod system becomes affected as well and the disease proceeds towards a total cessation of the retinal function. The early attack on the cone system naturally explains the severe impairment of the central visual acuity and is, furthermore, reflected by the grave disturbance in colour vision.

It is tempting to make a comparison with retinitis pigmentosa, in which disease the rod function, in particular, is severely affected from the beginning. The main feature of the clinical picture is the lesion to the periphery of the retina resulting in contraction

of the visual field and night-blindness, whereas the macula may continue to function almost satisfactorily for a considerable time. Hence the above-mentioned degeneration of the retina in hereditary ataxia is of quite another type and clearly distinguished from the retinal degeneration known from retinitis pigmentosa.

It has not been possible to find in the literature on the subject any earlier cases of hereditary ataxia that have been examined by means of E.R.G. However, several cases of ophthalmoscopical fundus changes have been reported. In the material brought together by Sjogren (1943), which comprises 188 cases from 118 Swedish families, macular changes occurred in three cases and more extensive changes in the fundi in another three cases (70 Ea, 71 Ea, 72 Ea, and 51 a, 58 a, and 61 a, respectively). In some of these cases the fundus changes are probably due to inflammatory processes. One (72 Ea) of the cases showing degeneration of the maculae belongs to the same family as our Cases 3 and 5.

Franceschetti and Klein (1948), in a critical survey of retinal degeneration in hereditary ataxia which included all cases published up to that date, have tried to exclude cases of inflammatory origin and cases where the diagnosis seemed doubtful. The remaining material consists of 22 cases of retinal degeneration belonging to 12 families. In some of them the fundus changes resembled those found in retinitis pigmentosa, in others there was a degeneration of the maculae. Often the clinical picture may be regarded as a combination of both types, and for these cases Franceschetti and Klein have coined the term "*retinite pigmentaire atypique*". In two of the 12 families there were extensive fundus changes resembling our findings in Case 5: in three siblings reported by Kapuściński (1934) and two first cousins reported by de Mello (1943) (quoted from Franceschetti and Klein, 1948). With the exception of the ophthalmological findings, however, the cases were quite different from those of the present study.

Franceschetti and Klein further discuss the question whether the simultaneous occurrence of retinal degeneration and hereditary ataxia is a random coincidence of two different diseases. However, they arrive at the conclusion that " les deux processus dégénératifs doivent etre considérés comme conséquence directe d'un facteur héréditaire commun".

Furthermore, it may be mentioned here that optic atrophy is said to be much more frequent than retinal degeneration in cases of hereditary ataxia. Of 100 cases, Sjogren (1943) found 22 cases of optic atrophy and, in addition, 17 cases where he found the papillae to be pale. In the material published by Bell and Carmichael, which includes all cases reported up to 1939, optic atrophy occurs in 9% (quoted from Greenfield, 1954).

It is not unique—nor is it very common so far as can be seen from the literature—that the impaired vision, as in our first two cases, constitutes the first symptom and causes the patient to see a doctor several years before the onset of other symptoms. As for the retinal degeneration in hereditary ataxia, Franceschetti and Klein (1948) point out as a characteristic feature that the visual symptoms first occur at the same time as other disturbances in the central nervous system.

It is a matter of great interest that for some years at the beginning of the disease the visual disturbance could not be given a satisfactory explanation founded on the routine methods of ophthalmological examination. Also the vague ophthalmological findings sometimes resulted in a diagnosis of degeneration of the macula, and sometimes in a diagnosis of optic atrophy. When reviewing the cases already published it is striking how few objective findings are actually made, even in cases of severe loss of vision. It is also striking to find that the diagnosis of optic atrophy is sometimes based only on a slight discoloration of the papilla, as has already been pointed out by Bell and Carmichael (1939). It is possible that some of the cases of impaired visual acuity hitherto attributed to primary optic atrophy ought rather to come under the category of retinal degeneration with consecutive optic atrophy. This would imply that degeneration of the retina is more common as a constituent of hereditary ataxia than has so far been believed. In future investigations into the problem of the origin of visual deterioration in hereditary ataxia, E.R.G. examinations of further cases should be of great value.

Summary

Five cases of hereditary ataxia with deterioration of vision are described. The cases belonged to four different families.

In four of the cases, the clinical examinations included single-flash electroretinography (single-flash E.R.G.) and flicker electroretinography (flicker E.R.G.), thereby revealing extensive retinal lesions. In these four cases, ophthalmological routine methods could not account for the impaired vision. In three of the cases, flicker E.R.G. was pathological at a stage when single-flash E.R.G. was normal or showed marginal values. In the fifth case, ophthalmoscopy revealed an advanced retinal degeneration.

Taken together, the results show that a comparatively uniform type of extensive progressive

retinal degeneration prevailed in the cases described. Both the cone and the rod systems were involved, though to a certain extent selectively, and it is suggested that the development of the disease is as follows. First, there is a disturbance of the cone function with progressively defective colour vision and visual acuity, while the rod function remains relatively intact. Later, the rod system becomes affected as well and the disease proceeds towards a total cessation of the retinal function.

Retinal degeneration in hereditary ataxia is probably more frequent than previously believed and may have constituted the cause of visual deterioration in some of the cases where hitherto it has been ascribed to primary optic atrophy.

References

Bell, J., and Carmichael, E. A. (1939). "*On Hereditary Ataxia and Spastic Paraplegia.*" *Treas. hum. Inher.*, vol. 4, pt. 3.

Bogaert, L. van (1948). *Rev. Oto-neuro-ophtal.*, **20**, 415.

Dodt, E., and Wadensten, L. (1954). *Acta ophthal.* (*Kbh.*), **32**, 165.

Franceschetti, A., and Klein, D. (1948). *Rev. Oto-neuro-ophtal.*, **20**, 109.

Granit, R. (1947). *Sensory Mechanisms of the Retina.* Oxford University Press, London.

Greenfield, J. G. (1954). *The Spino-Cerebellar Degenerations.* [American Lecture Series.] Blackwell, Oxford.

Kapuściński, W. (1934). *Ber. dtsch. ophthal., Ges.*, **50**, 13.

Karpe, G. (1945). *Acta ophthal.* (*Kbh.*). Suppl. 24.

—— (1948). *Docum. ophthal.* (*Paris*), **2**, 268.

—— (1955). Personal communication.

——, and Tansley, K. (1948). *J. physiol.* (*Lond.*), **107**, 272.

Mello, A. R. de (1943). *Arch. brasil. Med.*, **33**, 1. Quoted by Franceschetti and Klein (1948), p. 133.

Sjogren, T. (1943). "*Klinische und erbbiologische Untersuchungen über die Hereoataxien.*" *Acta psychiat. neurol.* Suppl. 27. Munksgaard, Copenhagen.

Wadensten, L. (1954). *Acta. ophthal.* (*Kbh.*), **32**, 743.

—— (1956). *Ibid.* In the press.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 194.

PAROXYSMAL DYSPHASIA AND THE PROBLEM OF CEREBRAL DOMINANCE

BY

H. HÉCAEN and MALCOLM PIERCY

From the Neurosurgical Centre, Hôpital Ste. Anne, Paris

The problem of the functional specialization of the two cerebral hemispheres has its origin in studies of aphasia. In a report which received little attention at the time, Marc Dax maintained (1836) that aphasia was associated with lesions of the left hemisphere. Broca admitted in his earlier writings that both hemispheres might be involved in language functions but in his later observations he insisted that the left hemisphere was dominant for this function. This suggestion was soon confirmed by the observations of Bastian, Hughlings Jackson, and Wernicke.

However, exceptions to this rule were soon noticed. In fact, as from 1865, Broca conceded that there might be a small number of individuals " who were exceptions and would speak with the right hemisphere ", and he approached present-day explanations when he wrote:

> " Just as there are left-handers in whom the inherent predominance of the motor activity of the right hemisphere confers a natural and irreversible predominance to the activity of the left hand, so in the same way it is conceivable that there may be a certain number of people in whom the inherent predominance of the convolutions of the right hemisphere will reverse the order of the phenomena which I have just described."

Broca thus emphasized the correlation between cerebral dominance and contralateral hand preference; left hemisphere lesions in right-handers and right hemisphere lesions in left-handers were supposed to result in aphasia.

But gradually, as evidence in contradiction to this principle arose, either in relation to aphasia (crossed aphasia) or in relation to agnosia, there developed a tendency to abandon the concept of absolute dominance and to substitute the idea of lateral dominance which was not necessarily the same for different functions, or else the idea of a simple functional predominance of one of the hemispheres. Thus Nielsen (1946) speaks of a major and minor hemisphere for a particular function, suggesting thereby a simple quantitative difference in functional potential between two symmetrical zones.

On the other hand, the question has been tackled from the point of view of the handedness of the subject. The classical rule (aphasia with left-sided lesions in right-handed patients; aphasia with right-sided lesions in left-handed patients) rapidly encountered exceptions which were designated " crossed aphasia ". Most of these anomalous cases were left-handers with right hemiplegia and it has been suggested that these were actually either ambidexters or left-handed people who had learned to write with the right hand. Crossed aphasia in fully right-handed people appears, however, to be much more rare.

Thus Ettlinger, Jackson, and Zangwill (1955) were able to trace only 15 published cases of dysphasia occurring in association with a right hemisphere lesion in ostensibly right-handed patients. Three of these were ambidextrous and in nine there was familial evidence of left-handedness. They state in fact that they could find only two well authenticated cases which were not ambidextrous and which had no familial left-handedness. The personal case reported by Ettlinger, Jackson, and Zangwill regarded himself as right-handed but appeared to have greater facility with the left hand than is usual in right-handed people.

Recent studies (Conrad, 1949; Humphrey and Zangwill, 1952) suggest that cortical organization for language is different in left- and right-handers. In fact, the study of aphasic left-handers shows that cerebral dominance is far from being as definite in left-handers as in right-handers, since in the former the lesion may sometimes be in the right hemisphere and sometimes in the left. Of the 18 aphasic left-handers of Conrad, 10 had a left-sided lesion, seven a right-sided lesion, and in one case the lesion was bilateral. In the 10 left-handed cases reported by Humphrey and Zangwill with unilateral cerebral damage to the supposed language area, dysphasia in a permanent form was present in five subjects, with left-sided lesions and in only one of the five subjects with a right-sided lesion. Moreover, the

severity of the disturbance was less in the second group.

Wepman (1951), on the basis of his personal cases and a critical review of cases in the literature, reached the radical conclusion that permanent aphasia depends solely on left hemisphere lesions irrespective of manual preference.

In a recent paper on aphasia in left-handers, Goodglass and Quadfasel (1954) on the basis of 13 personal cases and 110 cases in the literature made a more refined analysis and drew more cautious conclusions. They found that in left-handers 50 out of 62 cases with right hemisphere lesions and 53 out of 61 cases with left hemisphere lesions suffered a dysphasia.

Their material suggests that aphasia following a lesion in the hemisphere ipsilateral to the preferred hand is much more frequent in left-handers than in right-handers, since aphasia occurred following a left cerebral lesion in 80% of the left-handers studied. For these authors, there is no direct and necessary relationship between manual preference and cerebral lateralization of language functions; they maintain that left cerebral dominance is more general than right-hand preference and that right cerebral dominance is much less frequent than left-handedness.

It might be added that, to the extent that their data is a fair sample of left-handed patients with appropriately situated unilateral lesions, it can be concluded that many left-handed people have bilateral representation of language. For both the left-sided and the right-sided lesions the incidence of dysphasia significantly exceeds 50% (80% and 86% respectively). Such a degree of overlap is not consistent with unilateral representation of language in most left-handed people.

All of these studies have been concerned with dysphasia occurring in association with a permanent cerebral lesion. We have undertaken a study of paroxysmal dysphasia in the hope that the theoretical position as to cerebral dominance for language functions might be advanced a little further by an analysis of the incidence of dysphasia which occurs in association with an abrupt and short-lived disturbance of cerebral function. The present communication reports evidence concerning the incidence of such paroxysmal dysphasia occurring as an aura to an epileptic fit or as an epileptic equivalent. This has been studied in relation to the laterality of the focus of cerebral disturbance and in relation to the handedness of the patient.

Incidence of Paroxysmal Dysphasia

The examination of the case records of patients suffering from epileptic auras or equivalents was carried out with the aid of a punch-card system. Punch-card records had been kept of all patients seen in the service since 1947. All these patients had been examined by one of the authors (H. H.) and all the cards had been punched by the examiner. All cards punched for "epileptic aura or equivalent" were selected and from these were selected all cards punched for unilateral focus of cerebral dysfunction involving the cerebral cortex or the subcortical white matter. The detailed case notes of these patients were then examined to verify the evidence for epilepsy and for the localization of the cerebral disturbance. Only cases which conformed to at least two of the following criteria were accepted as having unilateral cerebral dysfunction: (1) Jacksonian type seizures; (2) cerebral pathology verified at operation or necropsy; (3) unilateral sensory or motor signs on clinical examination; (4) unequivocal lateralized E.E.G. focus; (5) unilateral lesion demonstrated by air-encephalogram or arteriogram.

Over 3,000 cases were checked with the punch-card system and of these 126 were found, on reference to the detailed case notes, to have had epileptic auras or equivalents and to conform to the criterion defined above as to the localization of the focus of cerebral dysfunction; 97 of these were right-handed and 29 were either left-handed or ambidextrous. Table I shows the incidence of paroxysmal dysphasia in these cases, occurring during an epileptic aura or equivalent. Expressive dysphasia in the table refers to a severe interference with speech and in most cases amounted to a complete aphemia. Receptive dysphasia refers to either a severe defect of auditory comprehension (temporary deafness excluded) or an alexia. Only two cases had such a paroxysmal alexia. With the exception of one right-handed patient with a left temporal lesion, all cases that presented a receptive defect also presented an expressive defect.

TABLE I
INCIDENCE OF PAROXYSMAL DYSPHASIA

	Side of Epileptic Focus	Left		Right	
	Type of Dysphasia	Expressive	Receptive	Expressive	Receptive
Right-handers	Aura with dysphasia	31	14	4	1
	Aura without dysphasia	31		30	
	Total aura	63		34	
Left-handers	Aura with dysphasia	17	1	9	1
	Aura without dysphasia	1		2	
	Total aura	18		11	

Expressive Defects.—The most striking finding which emerges from these results is the fact that,

although only 31 out of the 63 right-handed cases with left hemisphere dysfunction had paroxysmal expressive dysphasia, as many as 17 out of the 18 left-handed cases with similar cerebral pathology had a paroxysmal expressive dysphasia. This difference in the incidence of dysphasia between the left-handers and the right-handers is statistically significant on a χ^2 test ($\chi^2 = 11{\cdot}1$, $P < 0{\cdot}001$). In the case of right-sided cerebral dysfunction, the incidence of expressive dysphasia is again more marked in the left-handers (nine out of 11) than in the right-handers (four out of 34). This latter observation is, of course, consistent with the theories which attribute right-sided cerebral dominance for language to left-handers. However, the findings for left-sided dysfunction mentioned above are in apparent contradiction to such theories. Moreover, when the results for the left-handers are examined in isolation it is seen that the side of the responsible focus has no obvious effect on the incidence of paroxysmal dysphasia: 17 out of 18 for left-sided lesions as against nine out of 11 for right-sided lesions. Furthermore, it is noteworthy that in both groups of left-handers (left-sided lesions and right-sided lesions) the incidence of dysphasia is well above 50%. This fact makes it extremely improbable that the results for left-handers could be accounted for in terms of some left-handers being left hemisphere dominant for language and others being right hemisphere dominant. The amount of overlapping is great enough to suggest that most left-handers are liable to have a paroxysmal dysphasia from a focus of dysfunction situated in either hemisphere. This is consistent with Goodglass and Quadfasel's (1954) material on permanent dysphasia in left-handers.

In contrast to this stand the results for right-handers. A left hemisphere focus results in a paroxysmal expressive dysphasia in 31 out of 63 cases, whereas a right hemisphere focus results in paroxysmal dysphasia in only four out of 34 cases. If the left- and right-handers are compared irrespective of the side of the focus, it is seen that, whereas 61 out of the 97 right-handers have no dysphasia during their aura or its equivalent, this can be said of only three out of the 29 left-handers.

Thus it is clear that when an epileptic aura or equivalent occurs as a result of unilateral cerebral dysfunction it is very much more likely to be associated with a paroxysmal dysphasia in left-handers than it is in right-handers, irrespective of the side of the focus. It would seem also that in right-handers the side of the focus is much more relevant to the incidence of paroxysmal dysphasia than is the case in left-handers.

These results must be considered in relation to the special nature of the disturbance which occurs if they are to be reconciled with existing evidence as to cerebral dominance for language based on observations of permanent dysphasia. This is considered more fully below.

It may be noted that in the cases reported here there is an unusually large proportion of left-sided lesions both for left-handed and for right-handed patients. This suggested to us the possibility that epileptic auras and equivalents may be more common with left-sided than with right-sided foci. Accordingly the punch-cards were again checked and all cases with adequately localized unilateral cerebral lesions were selected and these cards were divided into two groups according to the side of the lesion. Each of these two groups was divided into two groups corresponding to the presence or absence of epileptic auras or equivalents. The result is shown in Table II.

TABLE II
CONTINGENCY OF INCIDENCE OF AURA UPON SIDE OF LESION

	Lesion		
	Left	Right	Total
Aura present ..	81	45	126
Aura absent ..	142	146	288
Total	223	191	414

$\chi^2 = 9{\cdot}2$ $P < 0{\cdot}01$

where the contingency of incidence of aura or its equivalent upon the side of the responsible lesion is found to be statistically significant ($\chi^2 = 9{\cdot}2$, $P < 0{\cdot}01$). There is no significant difference between the total incidence of left- and right-sided lesions ($\chi^2 = 2{\cdot}4$, $P > 0{\cdot}1$).

It is thus clear that a disturbance of the left hemisphere is particularly apt to result in the sequence of cerebral events involved in an epileptiform aura or its equivalent. Presumably the behaviour and experience which is disturbed during an aura is more profusely represented in the left than in the right hemisphere and so paroxysmal left hemisphere dysfunction is more liable to produce clinically obvious changes.

Receptive Defects.—It is immediately apparent from Table I that a paroxysmal receptive dysphasia during an aura or its equivalent is a less frequent occurrence than is a paroxysmal expressive dysphasia. Receptive paroxysmal dysphasia would also appear to be particularly infrequent in left-handed patients (1/18 with left-sided lesions; 1/11 with right-sided lesions). In the case of right-handed patients the frequency of receptive dysphasia is related to the

side of the lesion (14/63 with left-sided lesions as against 1/34 with right-sided lesions). Thus the results concerning receptive defects resemble those concerning expressive defects in that the incidence of the defect is related to the side of the lesion in right-handers but not in left-handers, but differ from them in that receptive defects are less frequent in left-handers than in right-handers whereas expressive defects are more frequent in left-handers than in right-handers.

Exceptional Cases

It is of some interest to consider in more detail the cases which depart from two of the general principles suggested above: (1) that a paroxysmal receptive dysphasia is very rare in left-handed patients; (2) that any kind of paroxysmal dysphasia is very rare in association with right-sided lesions in right-handed patients.

Left-handed Cases with Comprehension Defect.—Two of our left-handed patients showed a definite comprehension defect. One other patient was unable to understand what was said to him during the aura but questioning made it clear that this was a complete paroxysmal deafness and was not specific to language comprehension. This case is not reported here.

In the first of these two cases with comprehension defect there was a tumour of the posterior part of the left temporal lobe (oligodendroglioma). The epuivalents consisted of an abrupt inability to speak, understand, or read. Pre-operatively the only permanent language difficulty was a very mild amnesic dysphasia. However, two years after the operation there was a considerable degree of amnesic dysphasia, a literal alexia without agraphia, paralexia in reading words, and an agnosia for colours. Verbal comprehension was consistently intact, even for complicated orders. The patient was also able to imitate correctly the movements of the examiner in Head's hand-eye-ear test.

The other case was a patient with a right temporal glioma who had generalized convulsions and loss of consciousness. After a few weeks these changed in character. The seizure started with numbness of the left hand leading to numbness of the whole of the left side of the body. At the same time his speech became indistinct and he was unable to understand what was said to him. Except for difficulties occurring during seizures, the only disturbance of language was mild word-finding difficulties on naming tests and a dysgraphia which was marked by both literal and verbal errors. There was a mild constructional apraxia. At no time were there any difficulties of language reception apart from during seizures. There was reduced muscular tone on the left side (*hemihyperextensibilité* of André Thomas) but no disturbance of sensation.

These last two cases would appear to be of special interest in so far as there is a complete absence of permanent comprehension difficulty although the lesions were extensive, progressive, and involved the temporal lobe. Comprehension defects were, however, present in a paroxysmal form during epileptic equivalents and these are our only cases of left-handed patients showing a paroxysmal receptive defect of language.

Right-handed Cases with Right-sided Lesions.—Four right-handed patients showed a disturbance of language functions during an aura or equivalent resulting from a right hemisphere disturbance. In one of these cases (right temporal trauma) there was no true comprehension defect but a total deafness followed by tinnitus. The patient was, however, unable to speak. Ventriculography, E.E.G., and neurological examination all confirmed the right-sided focus of the lesion.

A second case (right temporal angioma) showed an unusual disturbance of language functions. In addition to a defect of articulation, which on occasions amounted to a complete aphemia, the patient, although able to understand what was said to him, reported that he could no longer " mentally deal with the rhythm of a sentence " and could not " imagine the sounds and pronunciation of words ". The patient's description of his difficulty (quoted above) raised the possibility that this was largely a feeling of unreality involving the words and sentences which he read or imagined. This suggestion is supported by the fact that the patient also reported feelings of unreality which did not involve language.

The third observation in this group concerns a child of 12 who had had convulsive seizures for nine years following an anti-typhoid inoculation. These seizures were preceded by paraesthesia starting in the left thumb and spreading to the left side of the face. Clonus of the left upper limb followed and the fit then rapidly generalized. After a series of fits the child remained mute for two days but without any receptive difficulty. After each isolated fit she also showed some dysarthria of brief duration. The E.E.G. showed diffuse changes and the air-encephalogram was normal.

In these three cases of right-handed patients with right cerebral hemisphere disturbances there was definite disturbance of verbal expression. The fourth case, however, is exceptional. A right-handed patient, aged 50, with no left-handedness in the family, since the age of 2 had had fits which started with clonus of the left superior limb. These

were succeeded at the age of 34 by equivalents which involved a complete aphasia: " I did not understand the person who was speaking to me for several minutes ", said the patient, " and I myself could not express my thoughts except for ' yes ' and ' no ' ". Neurological examination revealed reduced muscular tone on the left side. The E.E.G. showed anomalies (a form of spike and wave) restricted to the right hemisphere. Skull radiographs showed calcification involving an area the size of a half-crown in the right posterior parietal region. Thus, in the first three cases of this group, the motor disturbances were the only disturbances of language and can possibly be described as " arrest of speech " rather than as genuine language disturbance. However, it must be emphasized, on the basis of the last observation, that it is possible for receptive language functions to be disturbed in a paroxysmal fashion in association with a right cerebral lesion in a right-handed patient.

Permanent Cases

For purposes of comparison we now present the observations made on 12 left-handed patients (all using the right hand for writing before the illness or accident) with a unilateral cerebral lesion involving the language area (as verified at necropsy, operation, or—in one case—on the basis of associated clinical evidence). These 12 cases comprise all left-handed patients with appropriate lesions who were seen in the neurological service during the period covered by the investigation of paroxysmal dysphasia. Two of these 12 cases had a paroxysmal dysphasia during an aura or its equivalent and are included in the results reported above.

Table III shows that, regardless of which hemisphere is involved, comprehension difficulties are very rare. In fact, such difficulties were present in only one case in a permanent form, and in this case were only moderate in severity. In two other cases comprehension difficulty was present in a transitory or paroxysmal form. Word-finding difficulties were more frequent since they occurred in a permanent form in five cases with left-sided lesions and one case with a right-sided lesion, and in a paroxysmal or transitory form in one case with a right-sided lesion. Agraphia occurred in a permanent form in two cases (one right-sided lesion, one left-sided lesion) and was doubtful in two other cases. Dyslexia was observed in one patient with a right-sided lesion and in three with left-sided lesions and was doubtful in a fourth case with a left-sided lesion.

On the other hand, irrespective of the site of the lesion, anterior or posterior, right or left, verbal expressive difficulties were observed in all but one of these cases in a greater or lesser degree, usually only in a paroxysmal or transitory form. These observations thus evince the mildness of permanent aphasic manifestations in left-handed people regardless of which hemisphere is damaged. The conservation of comprehension in all of these patients except one is very striking when compared with the incidence of expressive difficulties. This is in accordance with the evidence obtained from the data on epileptic auras in left-handers. It is worth mentioning also that constructional apraxic difficulties were fairly marked and permanent in these cases, both with left and right hemisphere lesions.

Conrad (1949), Humphrey and Zangwill (1952), and Goodglass and Quadfasel (1954) suggest that in left-handers cerebral lesions involving the so-called language area involve aphasic difficulties which in general are more transitory and less severe than in right-handers, and this irrespective of the hemisphere

TABLE III*

LANGUAGE DEFECTS IN LEFT-HANDED PATIENTS

Case	Expression	Comprehension	Word-finding	Writing	Reading	Localization of Lesion
Left-sided lesions						
P (No. 1)	+	0	+ (Pa, Pe)	0	0	Temporal
L (No. 2)	++	+	++	0	0	Temporal
D (No. 3)	++ (Tr, Pa)	0	0	0	0	Unilateral
S (No. 4)	+++ (Tr, Pa)	0	0	±	±	Temporo-parietal border
F (No. 5)	++	0	0	+++	+	Parietal
B (No. 6)	+ (Pa)	+ (Pa)	+++	0	+	Postero temporal
H (No. 7)	0	0	++	±	0	Temporal (lobectomy anterior 2/3)
He (No. 8)	+ (Tr)	0	+	0	+++	Unilateral
Right-sided lesions						
N (No. 9)	+ (Tr)	+ (Tr)	+ (Tr)	0	0	Postero parietal
B (No. 10)	+ (Pa)	0	+	++	0	Temporo-parietal
P (No. 11)	+ (Pa)	0	0	0	0	Parietal (1st and 2nd convolutions)
G (No. 12)	++ (Tr, Pa)	0	0	0	++	Parieto-temporo-occipital border

Tr = Transitory Pa = Paroxysmal Pe = Permanent
Definite defects are marked with + and doubtful defects with ±.
Defects are permanent unless otherwise stated.

* This table has previously been published in a modified form (Hécaen and Ajuriaguerra, 1955).

involved. Our personal experience confirms this point of view, although, in the case of permanent dysphasia, our figures are small and valid comparisons are difficult to make. In this context we may refer to Case No. 4 in the table, who showed, following severe cranial trauma, a paresis of the right arm and an aphemia which had persisted for several months but which remitted almost completely. This patient, who was left-handed but wrote and drew with the right hand before the accident, easily learned to write and draw with the left hand after the accident. He had fits preceded by an aphemic aura, without any difficulty of comprehension. Examination 16 years after the accident revealed a slight right pyramidal deficit associated with a gross sensory deficit of the right upper limb, a doubtful dyslexia and dysgraphia and a slight ideomotor apraxia. An operation carried out for the relief of the concomitant fits revealed an obvious area of cortical atrophy involving the left-parieto-temporo-occipital border with an area of cortico-meningeal adhesion immediately anterior. The aura preceding the fits was reproduced by stimulation of the post-central gyrus and an area corresponding to the sensory region of the arm was excised. There was no aggravation of language difficulties after the operation.

It is difficult to make a comparison between the duration of expressive aphasia in right- and left-handers following anterior cortical ablation (pre-central gyrus) for epilepsy or abnormal movements since, in both types of case, the disturbance clears up very rapidly. However, it seemed to us that in two such left-handed patients the disappearance of the dysphasic disturbance after the operation was particularly rapid and complete.

Discussion

Previous work on cerebral dominance for language functions has been almost exclusively concerned with the chronic disturbance in language functions which accompanies a permanent cerebral lesion. The present study has been concerned with an acute and short-lived disturbance of normal function, and it is reasonable to seek an explanation of the differences between the results reported here and those obtained by previous workers in terms of the differences in the physiological disturbance that has been studied. Our results are in complete accord with previous work in so far as they reveal a marked left hemisphere dominance for language in right-handed people. Our results concerning expressive dysphasia in left-handed patients are, however, at variance with the usual findings. Not only is paroxysmal expressive dysphasia in left-handers as frequent with left hemisphere disturbance as with right hemisphere disturbance, but also the incidence of such a dysphasia in left-handers is much higher than in right-handers, irrespective of the hemisphere involved.

It has been suggested that dysphasia in left-handed patients with left-sided lesions is far from an exceptional observation (Humphrey and Zangwill, 1952; Conrad, 1949; Roberts, 1951; Goodglass and Quadfasel, 1954) and some authors have suggested that language may be more equally represented in the two hemispheres in left-handers than is the case with right-handers (Subirana, 1952; Chesher, 1936). Another observation which has been reported by more than one author is that recovery from dysphasia is more complete and more rapid in left-handers than in right-handers. This would, of course, be consistent with a more balanced cerebral representation of language with respect to the two hemispheres. Goodglass and Quadfasel tentatively suggested that left-handed people are more liable to a dysphasia than others, irrespective of the hemisphere damaged. However, the allegedly more transient nature of the dysphasic disturbances in left-handers would seem to point, in one sense, to relative invulnerability.

There is now fairly general agreement that it is not uncommon to find left-handed patients suffering from dysphasia in association with left-sided lesions and it has long been generally recognized that right-sided lesions may produce a dysphasia in left-handers. Similarly, numerous cases have been cited where there is no dysphasia in left-handers, although an adequate unilateral lesion is present. Such a lesion may be either in the left or in the right hemisphere. It would appear that a unilateral lesion in either hemisphere may or may not produce a dysphasia in a left-handed patient. The negative cases in left-handers do not appear from the literature to be markedly more frequent with respect to one hemisphere than with respect to the other, but these negative cases certainly appear to be more frequent in left-handers with right hemisphere lesions than in right-handed patients with left hemisphere lesions. It is probably not an exaggeration to say that the evidence concerning permanent dysphasia favours the suggestion that a left-handed patient with a unilateral lesion of either hemisphere has a better chance of escaping a dysphasia, or of recovering from it more rapidly, than a right-handed patient with a left hemisphere lesion.

Ettlinger and others (1955) maintain that the negative cases of left-handed patients with unilateral lesions of the language zones imply " strictly unilateral representation of speech . . . in some sinistrals at least ". However, although negative cases are of great importance, these authors'

conclusion is probably not an inescapable one. Bilateral representation of language does not *a priori* imply that a dysphasia must result if there is a unilateral lesion to the language area. It could equally be the case that bilateral language representation involves a certain degree of " equipotentiality " which would afford relative invulnerability to a unilateral lesion. The alleged mildness and transitoriness of dysphasia in left-handed patients is, in fact, consistent with such a possibility.

Our present findings stand in contrast to the evidence from permanent dysphasia discussed above. Ictal expressive dysphasia is more frequent in left-handed than in right-handed patients irrespective of the side of the unilateral cerebral disturbance. It is, however, possible that differences in the cerebral organization of language in right-handed and left-handed patients are such as would be consistent both with the evidence as to permanent dysphasia and with the evidence reported here. In the case of our results, the dysfunction was of abrupt onset and almost certainly of too short duration to permit any kind of cerebral adaptation to the interference. In the case of permanent dysphasia, however, the disturbance of language that is observed is the product both of the defect produced by the lesion and of any restitution of function resulting from compensatory activity of undamaged cerebral areas. The first type of observation may be compared to an immediate breakdown and the second to a more or less imperfect repair. Certainly, there is no necessity to assume that the sensitivity of a mechanism to acute interference is positively related to its incapacity for recovery. For example, where radical re-learning of a skilled performance is called for, this is most easily possible when the previous learning has not led to a highly integrated and well established ability. On the other hand, learning which has not achieved the status of a well organized skill is much more liable to break down under temporary stress.

In the case of dysphasia one is concerned less with the level of integration of the skill in using language in left- and right-handers than with the possibility of differences between the two groups in the degree of anatomical focalization of the skill, and it is conceivable that when a function is organized within a comparatively restricted area it may be on the one hand more resistant to acute interference and on the other hand less capable of spontaneous recovery than when such a function is organized more diffusely with respect to cerebral anatomy. We already have some evidence to suggest that language representation is more equally distributed between the two hemispheres in left-handed than in right-handed people. A possibility that should not be overlooked is that the bilateral representation of language in left-handers is only one aspect of the increased diffusion of language organization in these subjects. That is to say, it is conceivable that in left-handers the mechanism of speech involves a greater area of cerebral tissue within a single hemisphere than is the case with right-handers. However, even if this assumption is not made, we are in effect postulating a greater degree of equipotentiality in the cerebral mechanisms for language in left-handed and ambidextrous people than in right-handed people. But in view of our results this supposition involves us in the further assumption that greater equipotentiality is likely to involve greater sensitivity to acute interference of relevant function. So far as we are aware there is no experimental evidence either for or against this suggestion.

Since the time of the acceptance in general principle of Hughlings Jackson's (1932) concept of a hierarchy of levels of organization within the nervous system, there has been a tendency to regard the " higher levels " of nervous function as the prime example of organization, a view that is encouraged by the complexity and intelligence of the behaviour which these structures make possible. Jackson himself did not view the matter in this way. For him the highest centres are " the ravelled end ", and he speaks of " the highest centres, which are the least organized ". We find it tempting to echo Jackson's general comment on the highest centres with special reference to the organization of language functions in left-handers: " . . . the most complexly evolving . . . but the least perfectly evolved ". Such a scheme of organization might be expected to be comparatively unstable in the presence of acute interference, but nevertheless, more capable of reorganization following injury than its " more organized " counterpart in right-handed people.

In this context we would mention that there are certain resemblances between the cerebral organization of language in left-handed people and that in children. Thus, in children, aphasia following a right hemisphere lesion is more common than it is in adults, recovery from aphasia tends to be more rapid, and expressive defects—far more frequently than receptive defects—characterize dysphasia in a child (Guttmann, 1942). These differences between child and adult are strikingly parallel to those between left-hander and right-hander. It is to be expected that cerebral language mechanisms are less differentiated in children than in adults; this may also be the case in left-handed people. A less marked degree of " encephalization of function " for language in left-handers might well be associated with a slighter resistance to acute disturbance but

greater plasticity in respect of spontaneous recovery following brain injury.

Finally, mention should be made of the incidence of receptive defects. These are clearly rarer in a paroxysmal form than are expressive defects and also appear to be rarer in left-handers than in right-handers. We do not feel that the tentative theoretical interpretation which we have advanced in relation to the expressive defects should be extended to explain the incidence of receptive defects. The results are, in fact, somewhat paradoxical. On the one hand, paroxysmal expressive defects are much more frequent in left-handers than in right-handers irrespective of the side of the lesion. On the other hand, both paroxysmal and permanent comprehension defects are rarer in left-handers than in right-handers. It is clear that further evidence is required before interpretation can be extended. However, on the basis of present evidence, we would suspect that the question of the degree of focalization of language function is likely to be crucial. This, in our view, has three aspects. First, there is good evidence to suggest more nearly equal bilateral representation of language in the two hemispheres in left-handed than in right-handed people. Secondly, it is possible that there are differences between the two groups in the diffuseness of language representation within a single hemisphere. Thirdly, there may be important differences in both left-handers and right-handers in the degree of cerebral focalization of language reception on the one hand and of language expression on the other hand. Without attempting to uphold a definite theory, we would suggest that the differences in the incidence of paroxysmal and permanent defects of language expression and reception in right-handed and left-handed patients may be more fully understood when more is known of the relative importance of the three aspects of focalization of function outlined above. It could be, for example, that language reception is generally more focally organized than language expression, that in left-handers this representation is bilateral, and that in left-handers all language functions are more diffusely organized within any one hemisphere than is the case with right-handers.

Summary

Current views on cerebral dominance for language are briefly reviewed on the basis of evidence from permanent dysphasia.

An analysis of the incidence of paroxysmal dysphasia occurring in association with epileptic auras and equivalents is reported. The data are analysed with special reference to the side of a unilateral focus of cerebral disturbance and to the handedness of the patient in 126 cases.

Paroxysmal expressive dysphasia occurred significantly more frequently in left-handed patients with aura than in right-handed patients with aura, irrespective of the side of the epileptic focus. In right-handed cases the incidence of expressive dysphasia was much greater in patients with left-sided disturbance than in those with right-sided disturbance. No such difference was observed in left-handed cases.

Paroxysmal receptive dysphasia was rare except in right-handed patients with left-sided cerebral foci. In this group the incidence was about half that of expressive dysphasia.

The findings are discussed in relation to evidence from cases of permanent dysphasia and it is suggested that the nature of the physiological disturbance involved may account for the differences between the results reported here and evidence based on cases of permanent dysphasia.

The tentative theoretical position is adopted that differences between left- and right-handed patients in the incidence and nature of dysphasia occurring in association with unilateral lesions or foci is consistent with differences between the two groups in the degree of cerebral specialization for language, both with respect to bilateral representation and with respect to representation within a single hemisphere.

Malcolm Piercy was supported in this work by a grant from the Centre National de la Recherche Scientifique, by arrangement with the Medical Research Council. This assistance is gratefully acknowledged.

References

Chesher, E. C. (1936). *Bull. neurol. Inst. N.Y.*, **4**, 556.
Conrad, K. (1949). *Nervenarzt.*, **20**, 148.
Ettlinger, G., Jackson, C. V., and Zangwill, O. L. (1955). *Journal of Neurology, Neurosurgery and Psychiatry*, **18**, 214.
Goodglass, H., and Quadfasel, F. A. (1954). *Brain*, **77**, 521.
Guttmann, E. (1942). *Ibid.*, **65**, 205.
Hécaen, H., and Ajuriaguerra, J., de (1955). *Aktuani Otazky v. Neurolog.*, II, 63.
Humphrey, M. E., and Zangwill, O. L. (1952). *Journal of Neurology, Neurosurgery and Psychiatry*, **15**, 184.
Jackson, J. Hughlings (1932). *Selected Writings of John Hughlings Jackson*, Vol. 2, p. 68. Hodder & Stoughton, London.
Nielsen, J. M. (1946). *Agnosia, Apraxia, Aphasia: Their Value in Cerebral Localization*. 2nd ed. Paul B. Hoeber Inc., New York.
Roberts, L. (1951). *Trans. Amer. neurol. Ass.*, **76**, 43.
Subirana, A. (1952). *Schweiz. Arch. Neurol. Psychiat.*, **69**, 321.
Wepman, J. M. (1951). *Recovery from Aphasia*. Ronald Press Company, New York.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 202.

THE PROLONGED AND DISTANT EFFECTS OF EXPERIMENTAL BRAIN INJURY ON CEREBRAL BLOOD VESSELS AS DEMONSTRATED BY RADIOACTIVE INDICATORS

BY

JAMES B. BRIERLEY

From the Department of Neuropathology, Institute of Psychiatry, Maudsley Hospital, London

The occurrence of oedema is a well-known clinico-pathological consequence of damage to the brain and is commonly regarded as an accumulation of tissue fluid resulting from an increased permeability of cerebral blood vessels. Experimental evidence that such vascular changes may occur far beyond the limits of the lesion is scanty. Prados, Strowger, and Feindel (1945) exposed an area of the cerebral cortex of cats to air for several hours and then injected trypan blue intravenously. The brain was removed the next day and showed, in addition to dark staining of the exposed cortex, a diffuse blue coloration of both hemispheres. Bakay (1955) observed (in autoradiographs) increased penetration of radioactive phosphate into the whole of a hemisphere that had received an injection of 1 to 3 ml. of molten paraffin wax a day previously. By the second day this evidence of oedema was restricted to a zone 2 mm. wide around the lesion.

Further evidence of remote effects was obtained by Tsang (1936) who ablated the rat visual cortex and demonstrated after varying survival periods that the lateral geniculate body on the same side was stained by intravenous carmine. This evidence of abnormal permeability was seen, in one instance, 153 days after the ablation.

Apart from these investigations, interest has centred largely on the local changes in permeability around lesions produced by such methods as coagulation of the intact dura (Caudill, Smith, French, Peyton, and Moore, 1951), coagulation of brain substance (Stern and Marshall, 1951; Broman, Radner, and Svanberg, 1949), stab wounds (Macklin and Macklin, 1920), and contusions (Syz, 1923; Stern and Marshall, 1951).

In the present investigation localized lesions of the rabbit cerebral cortex were produced by applying liquid oxygen to the intact skull, and the resulting changes in the cerebral vessels were detected after various periods of survival up to 14 weeks by injecting labelled di-iodo fluorescein (D.I.F.) and phosphate. The normal distribution of these substances in the rabbit nervous system has been reported previously (Brierley, 1953, *a* and *b*).

Methods

A single litter of healthy adult rabbits was used for each experiment. Three (or occasionally two) animals acted as controls. In the remainder lesions were made under nembutal anaesthesia by pouring liquid oxygen into a copper tube sealed on to the bare skull with vacuum grease (Fig. 1). The freezing time varied from 10 to 25 seconds depending on the level of filling (roughly from one-third to four-fifths full). The severity of the lesion was graded later when the brain was removed into "mild" (just visible), "moderate" (2-5 mm. diameter), and "severe" (6-8 mm. diameter). Recovery of consciousness occurred in one to three hours except after some severe lesions when it was delayed up to six hours with mild head retraction for up to a further

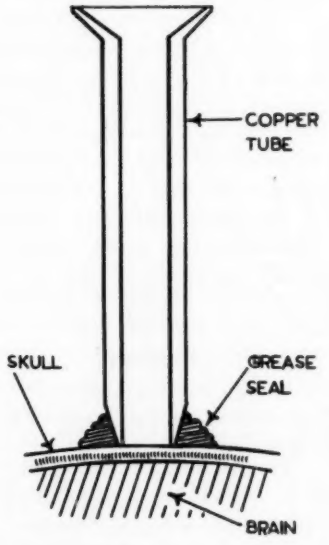


FIG. 1.—Vertical section of copper tube mounted on bare skull within grease seal. Length, 7 cm.; internal diameter, 1 cm.

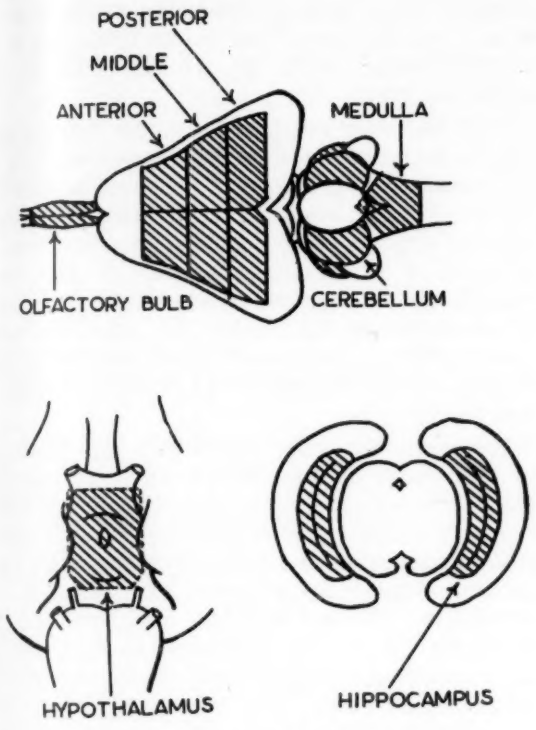


FIG. 2.—Diagrams of standard brain samples.

12 hours. No abnormalities in behaviour or motor function could be detected after a day and the skin incisions healed well. Freezing times of more than 25 seconds, however, were fatal.

After a period of survival which was different for each litter all the animals received a radioactive indicator intravenously. In the experiments with phosphate six litters were used and the animals (heparinized and under nembutal) received 10-250 μc. of ^{32}P in a small volume into an ear vein, and were allowed to survive for 10 minutes. Di-iodo fluorescein was given similarly to four litters in activities of ^{131}I from 170 to 850 μc. The survival period with D.I.F. was 15 minutes. The animals were killed by exsanguination. Samples of blood were taken (for radioassay of plasma or whole blood) on weighed dry filter paper discs (Reiss, Badrick, and Halkerston, 1949) which were then reweighed, dried in an oven at 100° C, and radioassayed under an end window counter. The brain and spinal cord were rapidly removed, cleansed of obvious blood and blood vessels, and sampled according to the standard plan shown in Fig. 2, except in one litter in which the cortex was divided into anterior and posterior portions only. In the case of the cerebrum and cerebellum, the sample consisted of thin slices excluding, as far as possible, the white matter.

After homogenization, in trichloroacetic acid for ^{32}P and in alcoholic caustic soda for D.I.F., the samples were assayed in M.6 liquid counters and a figure for the relative uptake of tracer independent of the actual radioactive dose was obtained from the ratio:—

$$\text{Tissue activity} = \frac{\text{Counts/min./100 mg. tissue}}{\text{Counts/min./100 mg. plasma}} \times 1000$$

In the first three litters of the phosphate series the terminal plasma activity was not used, but instead the estimated whole blood activity at the time of injection (Brierley, 1953a). This procedure does not affect the interpretation of the results.

Histological Examination.—The brains of a series of animals that had received lesions of various intensities were removed at intervals up to seven months. After fixation in 10% formalin each brain was divided coronally through the centre of the lesion, one half being embedded in celloidin and the other used for the preparation of frozen sections. Celloidin sections were stained by the techniques of Nissl, Heidenhain, Mallory (phosphotungstic-acid-haematoxylin), and Van Gieson. Frozen sections were stained by the silver carbonate method for microglia, of Holzer for fibrous glia, and of Herxheimer for fat.

Results

The detailed experimental results are given in Tables I and II. At each site the scatter in the control samples within a litter was small. Various ways of expressing the difference between control and experimental tissue activities were considered. In the end it was decided arbitrarily to take notice of values that were 20% or more greater than the highest control.

Immediately after the injury, a high concentration of both phosphate and D.I.F. was to be found within the lesion and in the adjacent cortex.

For phosphate (Table I) the maximum cortical ratios occurred at 15 minutes (31·7) and decreased steadily thereafter but were still considerable (13·0) at 14 weeks. Contralateral cortical activity was increased from the outset, attained a maximum at 48 hours (12·6), and was only slightly increased at 14 weeks (1·5). Hypothalamic and medullary ratios were greatest at 90 minutes (2·8 and 1·5) and had returned to normal at 38 days.

For D.I.F. (Table II) the high activities in the lesion declined sharply from 30 minutes to seven days and at 41days did not exceed 2·3. Contralateral cortical ratios, increased in all cases at seven days (maximum 11·6), were much reduced by 41 days (maximum 2·2). The brain-stem structures, hippocampus, and olfactory bulb showed maximum values at seven days and by 41 days only the hypothalamus and medulla had not returned to normal.

Throughout both series it was clear that the increases in tissue activity were greater with the more severe lesions. It is to be noted that the highest cortical values did not always occur within the lesion but might be found in either an adjacent ipsilateral segment or even in the contralateral cortex (Tables

TABLE I

VALUES FOR PHOSPHATE (^{32}P)*

Cortex								
Posterior		Middle		Anterior		Hypothalamus	Medulla	
L.	R.	L.	R.	L.	R.			
Survival 15 minutes								
12·5	14·6	14·2	15·3	15·8	13·9	10·7	12·0	Controls
14·5	16·2	18·2	16·6	16·6	14·2	11·4	13·7	
15·7	17·7	18·6	19·4	19·8	19·5	11·6	14·6	
354	14·6	*589*	24·2	43·1	22·0	20·9	16·1	Severe lesion
22·6		31·7	1·3	2·2		1·8		
316	86·2	*443*	71·6	576	30·3	15·0	14·3	Severe lesion
20·1	4·9	23·8	3·7	29·1	1·6	1·3		
310	16·6	*487*	16·5	49·7	20·1	16·4	13·8	Severe lesion
19·8		26·2		2·5		1·4		
124	16·0	54·2	14·5	15·5	15·9	15·1	—	Mild lesion
7·9		2·9				1·3		
Survival 90 minutes								
12·1	13·5	10·2	9·9	10·6	9·7	5·3	5·1	Controls
17·6	18·6	16·8	14·2	13·0	11·6	10·6	10·2	
485·2	25·8	75·9	31·9	21·1	22·2	29·7	14·9	Severe lesion
27·6	1·4	4·5	2·3	1·6	1·9	2·8	1·5	
112·8	14·6	42·0	19·6	24·0	18·8	16·7	14·5	Moderate lesion
6·4		2·5	1·4	1·9	1·6	1·6	1·4	
56·5	21·4	22·2	26·1	16·5	15·3	21·1	12·6	Moderate lesion
3·2		1·3	1·8	1·3	1·3	2·0	1·2	
23·3	20·5	*27·3*	33·8	16·8	26·2	16·6	13·9	Mild lesion
1·3		1·6	2·4	1·3	2·3	1·6	1·4	
Survival 48 hours								
9·3	8·0	8·1	9·2	7·7	7·9	7·7	6·5	Controls
10·2	8·6	9·6	9·4	12·3	9·3	7·8	8·0	
11·7	11·8	10·1	10·6	12·5	11·8	8·2	9·5	
58·2	87·7	95·5	133·0	49·5	15·2	10·3	8·1	Moderate lesion
5·0	7·4	9·5	12·6	4·0	1·3	1·3		
8·7	7·9	*16·1*	5·5	10·2	10·4	9·7	6·1	Minute
		1·6						
9·4	7·9	7·9	8·9	10·4	9·0	9·5	7·3	Nil seen
Survival 15-20 days								
20·2	20·0	18·5	19·2	22·6	19·8	16·8	22·4	Controls
22·1	20·2	26·4	28·3	25·1	22·3	16·2	23·4	
29·9	29·5	28·6	29·5	35·5	35·0	22·4	24·6	
27·2	18·0	*285·0*	20·0	27·6	24·9	20·3	17·6	Moderate
		10·0					0·8	
24·0	25·8	*201·0*	23·2	29·8	24·5	18·7	16·5	Moderate
		7·0					0·7	
16·9	20·4	*19·4*	18·4	24·1	18·0	17·1	20·0	Minute
Survival 36-38 days								
33·8	25·6	30·5	29·1	27·7	33·2	27·2	20·0	Controls
36·2	34·3	36·3	38·5	43·4	39·9	28·1	21·1	
117	30·0	*96·4*	10·8	20·4	34·0	36·2	29·2	Moderate
3·2		2·7				1·3	1·4	
36·1	31·1	*516*	30·8	42·0	63·2	29·8	24·8	Moderate lesion
		14·2			1·6			
68·1	34·1	48·8	37·3	48·3	55·7	38·6	29·0	Mild lesion
1·9		1·3			1·4	1·4	1·4	
Survival 14 weeks								
16·6	16·1	12·5	15·3	16·4	16·3	19·6	14·1	Controls
–	17·0	12·8	15·7	17·6	17·6	20·3	14·2	
18·1	17·7	17·9	17·7	19·4	18·1	20·5	15·4	
108	25·1	*233*	20·9	26·7	21·7	23·0	13·1	Moderate lesion
6·0	1·4	13·0		1·4				
21·3	25·7	*74·9*	21·6	23·0	—	23·1	15·3	Moderate lesion
	1·5	4·2	1·2					
21·8	21·4	*29·6*	21·7	25·9	18·5	23·0	14·9	Moderate lesion
1·2	1·2	1·7	1·2	1·3				
24·0	17·8	22·8	18·5	20·5	19·5	21·9	14·6	Mild lesion
1·3		1·3						

* In the tables all the values have printed below them the ratio of the experimental value to the highest control value (the smallest ratio found is therefore 1·2). When the sample included the lesion or part of it, the figure for tissue activity is printed in italics. The lesions were always placed in the left hemisphere. Each section presents the results from one litter.

I and II). These apparent anomalies may be ascribed in part to some loss of the frozen tissue due to its semifluid state (early) or its adherence to the meninges (late).

With the larger ratios it is apparent that the only way of accounting for the high concentrations of radioactivity in the specimens is to suppose that the tracer has passed out of the blood vessels as a result of a real increase in permeability. For lower ratios, however, it is necessary to consider two other possible factors, namely, transport of radioactivity in cerebrospinal fluid from the lesion to more remote parts of the nervous system and an increase in blood within the samples as a result of vasodilatation *in vivo*.

The role of the cerebrospinal fluid was eliminated by experiments on three rabbits with severe lesions. The survival periods were one, 19, and 24 hours before ^{32}P was given in the usual way. Cerebrospinal fluid was collected by cisternal puncture after eight minutes, and the animals exsanguinated at 10 minutes. At one and 24 hours there was no detectable ^{32}P in the cerebrospinal fluid, but at nine hours the activity referred to the terminal plasma activity in the usual way was 11, *i.e.*, less than normal cortex, but even this may have been due to a slight blood contamination which was noted. It is therefore considered that ^{32}P in the cerebrospinal fluid cannot account for even the smallest increase observed in the experimental samples.

Vasodilatation, however, proves to be of great importance, particularly in the interpretation of results with D.I.F. It has been shown previously (Brierley, 1953a) that in normal brain the vessels are virtually impermeable to D.I.F. and this substance had therefore been used to determine the amount of residual blood in the normal brain samples. After an intravenous dose of D.I.F. at least four-fifths of the radioactivity of normal brain samples can be removed by saline perfusion and the remaining one-fifth is bound to some tissue elements. It follows that to increase the total sample activity in the ratio 1·2 (the critical level adopted here) would require a vasodilatation *in vivo* sufficient only to increase the residual blood of the sample by 20%, providing there was no change in permeability. Then also, perfusion would be expected to remove four-fifths of the increased total activity and to leave a proportionately increased amount of " fixed " dye.

The actual situation was clarified in a litter of four animals, of which two acted as controls and two received severe lesions. All received D.I.F. as usual but, before taking samples, one of the lesioned animals was perfused with a litre of saline. The

TABLE II

VALUES FOR D.I.F.

Cortex						Hippo-campus	Medulla	Hypo-thalamus	Cerebel-lum	Cervical Spinal Cord	Olfactory Bulb	
Posterior		Middle		Anterior								
L.	R.	L.	R.	L.	R.							
Survival 30 minutes												
10·7				11·7			8·1	9·4	10·2	11·2		Controls
14·7				15·1			9·9	10·6	14·6	14·5		
373				160			18·8	35·8	13·8	22·9		Severe lesion
25·4				10·6			1·9	3·4		1·6		
556				56·2			15·5	16·6	18·6	12·2		Moderate lesion
37·8				3·7			1·6	1·6	1·3			
255				205			11·8	16·7	16·4	16·3		Moderate lesion
17·3				13·6				1·6				
Survival 7 days												
9·4	11·1	10·1	11·4	13·0	13·6	5·8	7·9	6·8	9·6		8·9	Controls
13·1	12·4	13·1	14·0	14·4	14·3	8·9	8·5	8·1	10·1		9·5	
14·0	16·1	15·1	16·3	15·0	15·0	9·1	10·1	10·3	12·8		11·0	
137	187	*196*	81·6	80·7	77·8	54·6	41·9	56·7	37·2		50·9	Severe lesion
9·8	11·6	13·0	5·0	5·4	5·2	6·0	4·2	5·5	2·9		4·6	
36·2	43·0	*91·7*	34·8	101	36·6	34·3	31·3	29·0	33·0		29·5	Mild lesion
2·6	2·7	6·1	2·1	6·7	2·4	3·8	3·1	2·8	2·6		2·7	
31·2	35·2	*31·6*	28·8	33·4	32·2	23·6	24·7	30·2	17·2		23·6	Very mild lesion
2·2	2·2	2·1	1·8	2·2	2·2	2·6	2·5	2·9	1·3		2·2	
18·3	26·0	*34·8*	19·6	25·2	18·8	15·0	13·0	15·2	21·0		18·8	Nil seen
1·3	1·6	2·3	1·2	1·7	1·3	1·7	1·3	1·5	1·6		1·7	
Survival 29-31 days												
8·7	8·9	4·9	5·4	10·6	12·0		6·0	6·5	6·2		7·2	Controls
9·8	9·0	7·6	6·7	11·8	12·4		7·1	6·8	7·7		9·0	
11·9	11·8	8·0	7·2	—	—		7·4	7·1	10·8		11·3	
12·7	9·4	*36·2*	16·7	10·2	10·2		8·8	7·3	10·6		15·5	Severe lesion
		4·5	2·3								1·4	
42·0	10·8	*25·1*	10·4	12·7	10·3		8·1	7·6	9·2		13·4	Moderate lesion
3·5		3·1	1·4									
16·7	13·2	*20·8*	11·8	11·2	14·1		9·3	8·9	11·1		11·9	Moderate lesion
1·4		2·6	1·6				1·3	1·3				
Survival 34-41 days												
8·7	8·9	4·9	5·4				6·0	6·5	6·2		7·2	Controls
9·8	9·0	7·6	6·7				7·1	6·8	7·7		9·0	
11·9	11·8	8·0	7·2				7·4	7·1	10·8		11·3	
24·6	17·5	*15·8*	15·1				9·6	10·7	8·1		—	Severe lesion
2·1	1·5	2·0	2·1				1·3	1·5				
22·0	13·2	*9·1*	10·3				10·4	10·6	9·7		10·2	Severe lesion
1·9			1·4				1·4	1·5				
15·7	9·5	*12·6*	15·8				10·2	9·0	11·8		8·5	Moderate lesion
1·3		1·6	2·2				1·4	1·3				
27·6	14·4	*16·6*	10·7				8·5	6·2	10·0		—	Moderate lesion
2·3	1·3	2·1	1·5									

results are given in Table III. Comparing the two cortical samples it is seen that considerable permeability to D.I.F. must have developed as only 28% of the radioactivity was removed by perfusion. In the hypothalamus and medulla 73 and 72% of the activity is removed by perfusion but the remaining "fixed" fraction is in each case greater than the total activity of the unperfused control samples and from 5·5 to 6·0 times greater than their "fixed" fractions. Thus in the experimental animal the raised sample activities may be interpreted as the result of vasodilatation *in vivo* which produces an absolute increase in residual blood but also an absolute increase in dye bound to tissue. Whether the latter includes some dye that has passed through the vessel wall and thus represents a true increase in permeability cannot be decided from the present data.

TABLE III

EFFECT OF PERFUSION ON EXPERIMENTAL ANIMALS D.I.F.

	Counts/min./ 100 mg.	Exp./Control	Exp./Control
Cortex (posterior)	10·8	11·4*	8·1*
Hypothalamus	7·9	4·4	1·2
Medulla	3·9	3·9	1·1
Animals	2 controls	severe lesion	severe lesion perfused

* Activities as multiple of control values.

In contrast to D.I.F., normal cerebral vessels are permeable to phosphate and the activity to be attributed to ^{32}P remaining in the blood vessels is relatively small. Brierley (1952) estimated this proportion as 20 to 27% using values for the residual blood of brain samples obtained with D.I.F. (Table IV). Direct perfusion experiments have confirmed this estimate (Table V). In a litter of six rabbits, two were ordinary controls, two were controls perfused before brain sampling, and two

TABLE IV

AVERAGE TISSUE ^{32}P ACTIVITIES (10 NORMALS) CORRECTED TO TERMINAL BLOOD ACTIVITY OF 1,000 C/MIN./100 MG.

	Counts/ min./ 100 mg.	Residual Blood/ 100 mg.	Residual Blood as Counts/ min./ 100 mg.	Residual Blood as % Total Count
Cortex (posterior)	31·0	0·629	6·29	20·3
Hypothalamus	29·7	0·722	7·22	24·3
Medulla	27·3	0·769	7·69	27·0
Spinal cord	30·4	0·845	8·45	27·8

were given severe lesions 48 hours previously and one of these was perfused before sampling.

Table V shows that perfusion reduced the activity of the samples by between 10% and 30% in both the controls and the experimental animals. In the latter, the activities remaining in the samples are greater than those of the unperfused controls in all cases, the ratios being 2.4 for hypothalamus and 1.8 for medulla. Here again the increased total activities may be regarded as evidence of vasodilatation *in vivo* and the raised residual fractions as due to the associated increase in phosphate penetration.

TABLE V

PERFUSION OF CONTROL AND EXPERIMENTAL ANIMALS: ^{32}P

	Counts/ min./ 100 mg.	% Counts Lost	Experimental/ Control	Experimental/ Control
Cortex (posterior)	36·0	10·4	18·5*	13·2*
Hypothalamus	26·8	23·0	2·8	2·4
Medulla	21·6	14·4	2·1	1·8
Animals	2 controls	2 controls perfused	1 severe lesion	1 severe lesion perfused

* Activities as multiple of control values.

Histological Appearances.—Three hours after freezing the damaged area was recognizable as a sector of cortex almost unstained in Nissl preparations. Neuronal and glial nuclei were just visible in the centre of the area while at the boundary between normal and frozen cortex there was a band of shrunken hyperchromatic neurones of which the apical and basal processes were stained for some distance beyond the cell body. Scattered throughout the lesion were numerous irregular spaces filled with a fine foam-like network and often continuous with greatly dilated perivascular spaces. The interpretation of these spaces was doubtful as either a colliquative necrosis of tissue or an escape of plasma from damaged vessels could be the causative factor.

The myelinated fibres immediately below the lesion were beaded and fragmented and presented a patchy, tigroid appearance under low power views. Small perivascular haemorrhages were sometimes seen in the boundary zone.

At one week the border of the lesion was sharply demarcated and phagocytic disintegration of the dead tissue had begun, as evidenced by the presence of fat-laden scavenger cells in the floor of the lesion. Within the boundary zone the microglia were activated but there was little change as yet in the astroglia.

During the next two to three weeks the salient histological changes were the complete invasion of the lesion by closely packed scavenger cells and the beginning of active mesodermal proliferation. The latter was seen as a fine collagenous network, particularly dense in the superficial part of the lesion adjacent to the meninges and spreading inwards as a more loosely arranged network. There was now a moderate increase in astrocytes (largely fibrous) in the boundary zone and a few patches of new capillary formation could also be recognized in the same region. The zone of hyperchromatic cells was somewhat reduced and lay parallel and close to the edge of the lesion.

From one month onwards there was surprisingly little change in the microscopic appearance of the whole glio-mesodermal scar whose content of fat-laden compound granular corpuscles seemed virtually unaltered even after seven months. Only the boundary presented evidence of a progressive process in the shape of an increasingly dense sheet of connective tissue separating the lesion from adjacent cortex and subcortical white matter.

In a few instances, patches of bone formation occurred in the depths of the scar and in general a certain number of hyperchromatic cells persisted in the cortex just outside the connective tissue layer. In this zone new capillary formation was at no time considerable.

In view of the wide distribution of the modifications in vascular permeability, careful search was made at all intervals after freezing for histological evidence of oedema in the cortex (outside the lesion), the diencephalon, and the brain-stem. In none of these regions at any time was it possible to identify the appearances described as characteristic of oedema by Greenfield (1952) and Jacob (1940). Thus demyelination of a patchy and partial nature occurs only in the white matter immediately subjacent to the lesion. Swelling of astrocytes was to be seen only in the boundary zone and at no time was marginal gliosis to be traced further than 1·5 to 2·0 mm. beyond the edge of the lesion. The perivascular spaces were not distended and the capillary endothelium appeared normal. Within the cortex there was no loss of cells and no changes were

evident in the intracortical axis cylinders or myelin sheaths.

Discussion

These experiments have revealed widespread increases in the content of radioactive D.I.F. and phosphate in the brain for many weeks after a cortical injury. In the region of the lesion there is a considerably increased amount of D.I.F. up to at least six weeks and of phosphate up to 14 weeks after freezing. These changes must be ascribed, at first, to the direct effect of low temperature on blood vessel walls and later to the abnormal permeability properties of the proliferating capillaries around the cortical scar. It is only in this region and during the first few hours that any histological evidence of oedema could be identified, all other parts of the brain appearing normal.

The raised activities in the contralateral cortex and in more remote parts, such as the medulla and hypothalamus, are most likely to be evidence of vasodilatation and its associated increased blood flow *in vivo*. A similar conclusion has been reached by Derrymaeker (1955) who carried out spectrophotometric assays of haemoglobin and trypan blue both in circulating blood and in nervous tissue from animals with experimental encephalitis, oedema, or cerebral allergy. Comparison with controls showed that while trypan blue in the tissue was increased, that of the contained haemoglobin was also increased but to a lesser extent. It was concluded that " . . . . this method shows the importance of vascular dilatation in the increased permeability of trypan blue ".

Caution should be exercised, however, in ascribing to an increase in vascular permeability any increase in the amount of an indicator in a sample even when allowance has been made for residual blood in the dilated vascular bed. It is quite possible that the permeability of a unit area of capillary endothelium may not have changed but that the total area of endothelium and the capillary blood flow have increased as a result of vasodilatation. It is therefore only permissible to regard the remote and persistent effects as more or less increased penetration of D.I.F. or phosphate from a dilated capillary bed into a standard mass of tissue.

The genesis of this vasodilatation is obscure and it is only possible to draw attention to a few factors that may have causal significance.

From within a few minutes of the restoration of normal temperature the centre of the lesion will be bathed in the fluid derived from the damaged vessels in the boundary zone. Various diffusible constituents of the necrotic tissue may be expected to enter this fluid, including adenylic compounds some of which, *e.g.*, adenylic acid and adenosine triphosphate, have a known vasodilator action. The extent of diffusion of such substances within the brain cannot be assessed but the role of the cerebrospinal fluid as a disseminator is suggested by the presence of adenylic compounds in it after concussion (Spiegel, Spiegel-Adolf, and Wycis, 1946).

Greig and Holland (1949) and Greig and Mayberry (1951) have presented evidence to show that the acetylcholine/acetylcholinesterase system is normally involved in the maintenance of capillary permeability. A possible connexion between a disturbance of this system and the permeability changes associated with brain injuries is suggested by the identification of free acetylcholine in the cerebrospinal fluid after closed head injuries by Bornstein (1946) and by Tower and McEachern (1949), who also demonstrated a depressed level of acetylocholinesterase.

The possible importance of neural connexions in the mechanism of the remote vascular changes has been demonstrated by Tsang (*vide supra*). The prolonged staining of the ipsilateral lateral geniculate body following ablation of the visual cortex was regarded as the vascular concomitant of retrograde cell change with its associated gliosis. In the present experiments, however, the lesion was too small to produce recognizable changes of this type in any subcortical region. The absence of such changes may not necessarily exclude the participation of neural pathways, particularly if the developing scar could be regarded as a source of abnormal impulses passing to lower levels and producing vasodilatation and increased blood flow, such as were demonstrated by Santha and Cipriani (1938) in subcortical structures as a result of cortical stimulation.

While no direct assessment of local changes in human cerebral vascular permeability is possible, indirect evidence may be found in the response to drugs of cases of head injury. The experimental studies of Aird, Strait, Zealear, and Hrenoff (1952) have shown that the concentration of cocaine hydrochloride in the cerebral cortex of concussed cats was greater than in controls. Barbour and Abel (1910) reported a lowered threshold to the convulsive substance acid fuchsin in concussed animals and Dandy and Elman (1925) noted a similar result for absinthe after cortical or subcortical lesions. In human cases the sedative and analgesic drugs might provide the most useful information as they are more likely to be employed in the management and aftercare of cases of head injury. Of particular value would be evidence of any exaggeration of response, reduced latency of action, or the appearance of atypical pharmacological effects.

Summary

A method employing liquid oxygen is described for the production of circumscribed lesions in the rabbit cerebral cortex.

Radioactive phosphate (^{32}P) and ^{131}I-labelled fluorescein (D.I.F.), injected intravenously, were used as indicators of vascular changes in nervous tissue.

One litter, divided into control and experimental groups, was used for each period of survival, which for ^{32}P was 15 minutes to 14 weeks and for D.I.F. 30 minutes to six weeks.

Within the lesion there was increased penetration of the indicators, diminishing in degree throughout the survival ranges. Smaller long-lasting changes occurred in the adjacent and sometimes the contralateral cortex and also in the hypothalamus.

Increased penetration into the medulla, hippocampus, and cerebellum was less constant and persistent.

The cerebrospinal fluid was shown not to contribute to the increased concentrations in brain substance.

The increased ratios outside the lesion were interpreted as the result of vasodilatation *in vivo*.

The evolution of the histological appearances of the lesion is described.

The significance of the experimental results is discussed.

The author records with pleasure his indebtedness to Professor A. Meyer for his interest and advice, to Dr. P. Merton for his critical perusal of the manuscript, and to Miss N. Billery and Mrs. B. Holder for their skilful assistance in the experimental, radioactive, and histological techniques.

References

Aird, R. B., Strait, L. S., Zealear, D., and Hrenoff, M. (1952). *J. Neurosurg.*, *9*, 331.
Bakay, L. (1955). A.M.A. *Arch. Neurol. Psychiat.* **73**, 2.
Barbour, H. G., and Abel, J. J. (1910). *J. Pharmacol.*, **2**, 167.
Bornstein, M. B. (1946). *J. Neurophysiol.*, **9**, 349.
Brierley, J. B. (1952). Proc. 1st Internat. Cong. Neuropath. Rome. Vol. III, p. 407.
——(1953a). Proc. Isotopes Technique Conference, 1951. Oxford. I. p. 224. H.M.S.O.
——(1953b). Unpublished results.
Broman, T., Radner, S., and Svanberg, L. (1949). *Acta psychiat.* (*Kbh.*), **24**, 167.
Caudill, C. M., Smith, G. A., French, L. A., Peyton, W. T., and Moore, G. E. (1951). *J. Neurosurg.*, *8*, 423.
Dandy, W. E., and Elman, R. (1925). *Bull. Johns Hopk. Hosp.*, **36**, 40.
Derrymaeker, A. (1955). *Excerpta med.* (*Amst.*), **8**, 845.
Greenfield, J. G. (1952). Proc. 1st Int. Cong. Neuropath., Rome, Vol. I, p. 107.
Greig, M. E., and Holland, W. C. (1949). *Science*, **110**, 237.
——, and Mayberry, T. C. (1951). *J. Pharmacol.*, **102**, 1.
Jacob, H. (1940). *Z. ges. Neurol. Psychiat.*, **168**, 382.
Macklin, C. C., and Macklin, M. T. (1920). *Arch. Neurol. Psychiat.* (*Chicago*), 3, 353.
Prados, M., Strowger, B., and Feindel, W. H. (1945). *Ibid.*, **54**, 163.
Reiss, M., Badrick, F. E., and Halkerston, J. H. (1949). *Biochem. J.*, **44**, 257.
Santha, K. von, and Cipriani, A. (1938). *Proc. Ass. Res. nerv. ment. Dis.*, **18**, 346.
Spiegel, E. A., Spiegel-Adolf, M., and Wycis, H. T. (1946). *Arch. Path.* (*Chicago*), **42**, 175.
Stern, W. E., and Marshall, C. (1951). *Proc. Soc. exp. Biol.* (*N.Y.*), **78**, 16.
Syz, H. C. (1923). *J. Pharmacol.*, **21**, 263.
Tower, D. B., and McEachern, D. (1949). *Canad. J. Res.*, Sect. E, **27**, 105.
Tsang, Y. C. (1936). *Arch. Neurol. Psychiat* (*Chicago*), **36**, 569.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 209.

MULTILOCULAR ENCEPHALOMALACIA*

BY

W. KRAMER

From the Department of Neuropathology, " Meer en Bosch ", Heemstede, Holland

The genesis of cavitation in the central nervous system presents an important problem. This holds true for porencephalia, syringomyelia, cystic tumours, Wilson's disease, and for cases of multilocular encephalomalacia. The last condition has been described under many different names which are summarized in Table I. I have accepted the name multilocular encephalomalacia as it combines in two words the main characteristics, namely the multiple cavity formation and the softening. Some investigators have concerned themselves solely with the anatomy and physiology of this condition (Edinger and Fischer, 1913; Jakob, 1931; Verhaart, 1936), but most papers have dealt with the pathogenesis.

TABLE I
NOMENCLATURE

Porencephaly (Heschl, 1859).
Encephalitis interstitialis congenita (Virchow, 1867).
Hydrocephalic porencephaly (Paltauf, 1901).
Child without forebrain (Edinger and Fischer, 1913).
Encephalodystrophia neonatorum (Siegmund, 1923).
Central porencephaly (Schwartz, 1924).
Polyporencephaly (Brocher, 1932).
Encephaloclastic porencephaly (Yakovlev and Wadsworth, 1946).
Multiple cystic softening of the brain in newborn (Lumsden, 1950).
Cystic degeneration of the brain (Benda, 1952).
Encephalomalacia with cavity formation (Ford, 1952).
Multilocular encephalomyelomalacia (Negrin and others, 1952).

I will summarize the findings of two cases of multilocular encephalomalacia which are interesting from an aetiological point of view.

Case Reports

Case 1.—The first child, a girl, of healthy parents was born by spontaneous vertex delivery. The mother was quite well throughout the pregnancy. Immediately after birth the child was motionless and only began to cry 24 hours later. After this she did not stop crying and slept only two to three hours a day. Soon after birth myoclonic jerks and epileptic fits started. She did not show any sign of psychic activity and the various types of epileptic fits continued in spite of anticonvulsive therapy. After a year she could swallow a little, but for the rest existed as a decorticated individual.

On examination at that age she showed the posture of decerebrate rigidity with a severe spasticity of both legs and there were athetoid movements of the hands. The skull was microcephalic and dolichocephalic. Tendon reflexes were exaggerated and there was a positive Babinski response on both sides. Laboratory investigations of the blood, cerebrospinal fluid, and urine showed no abnormalities. The Wassermann reaction was negative. At the age of 9 months an E.E.G. was made which showed almost no cortical activity whatsoever; only in the right parieto-occipeto-temporal region variations of the spike-and-wave complex, 350 microvolts in amplitude, were found.

As she became older the general condition steadily grew worse. She died at the age of 1 year and 9 months from progressive impairment of the vegetative centres of the brain. Post-mortem studies were performed three hours after death.

Necropsy Findings.—The hemispheres were reduced to a flabby sac which slowly collapsed after the escape of an enormous amount of C.S.F. through an artificial opening. Macroscopically the basal ganglia, brain-stem, and cerebellum appeared normal. The total weight of the brain was 270 g. only. The blood vessels were normal

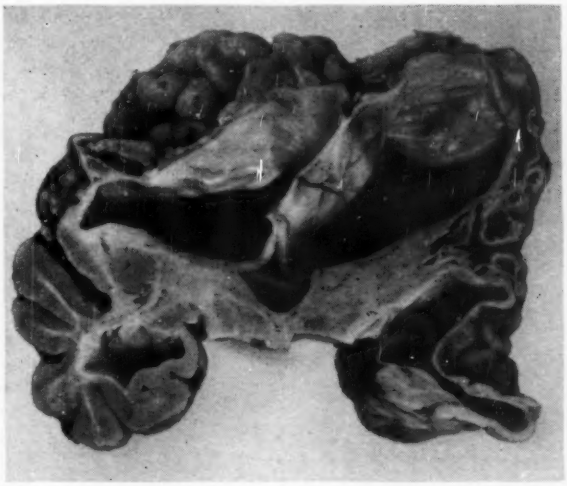


FIG. 1.—Transverse section through hemispheres of Case 1. Note the cysts in the white matter and the cortex and enormous dilatation of the ventricles.

* Communication delivered at the second International Congress Neuropathology, London, 1955.

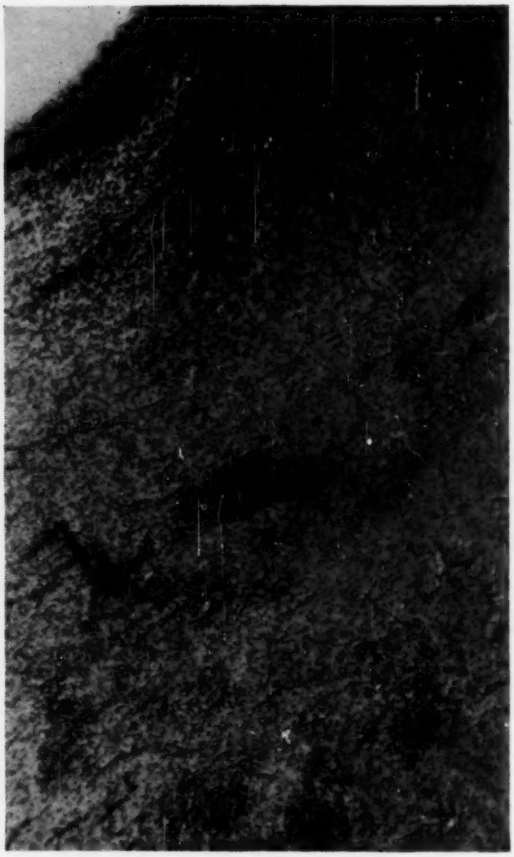


FIG. 2.—Subependymal nodules of embryonic cells.

FIG. 4.—Loosening of fibrous glial tissue of the white matter resulting in cavitation.

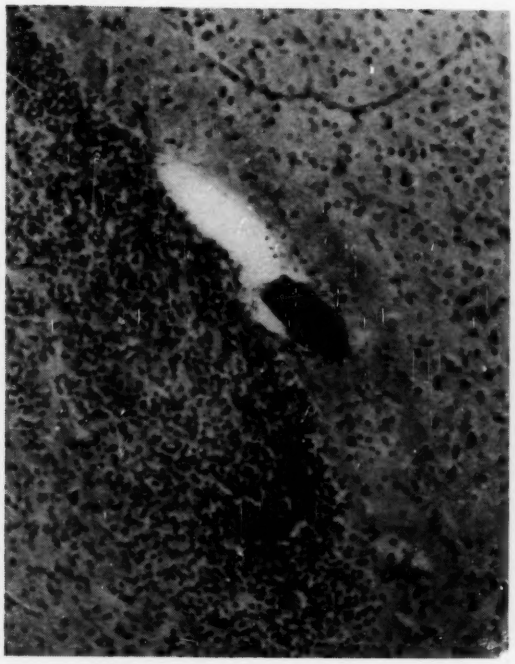


FIG. 3.—Group of immature cells in the neighbourhood of a blood vessel beginning cyst formation.

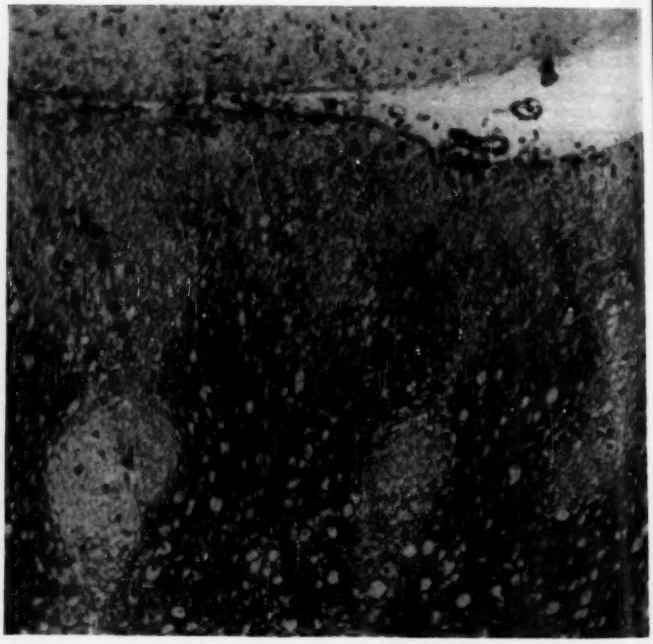


FIG. 5.—Invasion of the cortex by fibrous glial tissue of the white matter.

and there were no thrombi in the dural sinuses. On transverse section the ventricles proved to be greatly enlarged, while innumerable cysts were scattered throughout the white and grey matter of the hemispheres (Fig. 1).

The alterations of the brain mantle were more pronounced in the right hemisphere than in the left and in general they were severe in the zones that myelinate late, moderate in the intermediate areas of Flechsig (Bailey and von Bonin, Fig. 1, p. 7), and very slight in those zones that myelinate earliest. In the latter zones the cysts were confined to the white matter, whereas in the intermediate zones a severe microgyria (better " sclerogyria ") predominated. In the zones that myelinate still later there were no fissures and the pallium was transformed into a membrane.

Microscopic Studies.—The histological picture of the cysts as such did not differ much from that described by others. Some cysts were old and others more recent which made it evident that the process was still active at the time of death. This corresponds well with the clinical progress. In the neighbourhood of the ependyma of the anterior horns of the ventricles immature cells were found in great numbers. They were arranged in nodules, but were also more diffusely spread in the nervous tissue (Fig. 2). They could be traced from the ependyma into the direction of the cysts. Fig. 3 represents a small cavity at the border of a group of immature cells. It can be seen that the cavities do not develop exclusively around a vessel.

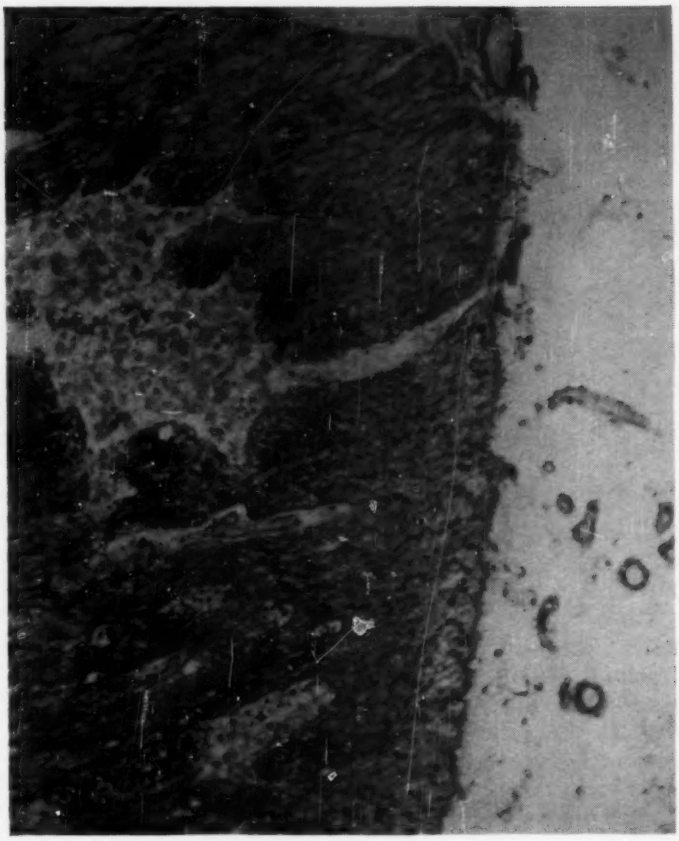


FIG. 6.—Softening of encapsulated cortical tissue resulting in cavitation.

Serial slides were made of large parts of the brain which demonstrate well that the walls of the vessels themselves were always normal. The same immature, small, dark-staining cells were also found in the walls of large cysts and in the cortex.

The white matter was nowhere normal. It consisted of a stroma of glia cells, in which fragmented and swollen nerve fibres were embedded. Immature cells, akin to those underneath the ependyma, were dispersed among more mature ones and signs of cell division were met with. Mitotic cell division was very rare, amitotic forms being more frequent.

Evidently cysts arose primarily in the white matter as the formation of cysts was often found underneath a relatively normal cortex, but never a cystic cortex overlying normal white matter. Within more or less normal white matter homogeneous spaces devoid of axons (Bodian stain) were met with, independent of the course of blood vessels. Such spaces were altered by interstitial oedema into a loose network of glial fibres, from which by hydropic degeneration small cysts were formed. Meanwhile, at the border of the cysts a capsule of glial fibres appeared. Fig. 4 shows a cyst with some fat granule cells amidst a loose network of glial fibres, surrounded by a dense glial fibrillary capsule.

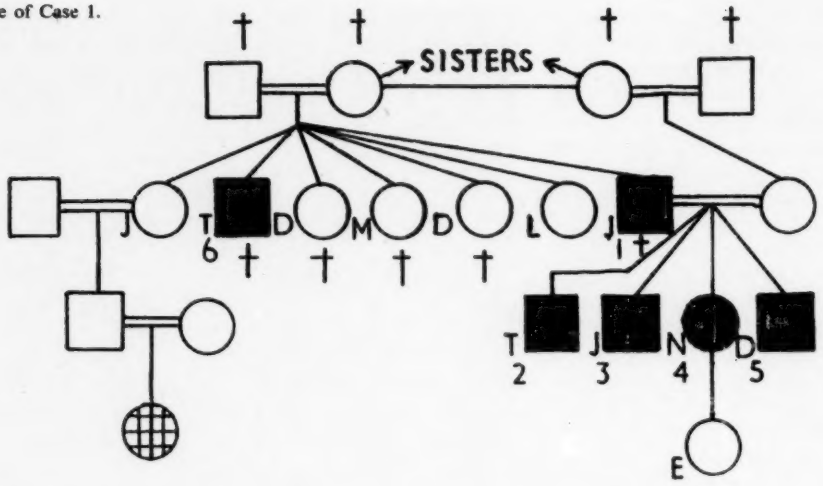
The relatively normal cortex had an embryonic appearance, as lamination was not distinct and nests of immature cells were present. A common finding was that the deepest part of the sulcus was not covered by a layer of cortex.

The cortical grey matter was invaded by fibrous glia cells, surrounding cysts in the white matter. Septa of fibrous glia isolated portions of cortical tissue (Fig. 5) which either underwent a process of softening and cyst formation or was replaced by a scar. Fig. 6 shows the fibrous glial tissue of the cortex, containing cavities filled with fat granule cells. It seems that these cells are transported to the perivascular spaces, the surrounding cysts, and the subarachnoid space. At last the cortex is replaced by a dense network of glia cells which show the same characteristics as those of the white matter between the cysts. Calcified neurons were found. The pia mater was thickened by an increase of collagenous fibres and was strongly adherent to the cortex. The blood vessels were normal and signs of inflammation were entirely lacking.

No lesions were found in the basal ganglia, the brainstem, or the spinal cord, except those resulting from secondary degeneration of the fibre tracts.

It happens that this child had an interesting family tree which was published by Biemond (1954). The cross-hatched circle (Fig. 7) represents this patient.

Fig. 7.—Family tree of Case 1.



Two uncles of the father suffered from spinocerebellar degeneration. Moreover four cousins of the father had some spinocerebellar disease.

The second case concerns the elder sister of the patient described under the title " Poliodysplasia Cerebri " (Kramer, 1953). The histopathological picture of poliodysplasia was the result of a disordered histogenesis, both of neurons and glial elements. These were under-developed and disorganized. A spongy disintegration of the fifth cortical layer was predominant, but the grey matter of the whole central nervous system was dysplastic and hypoplastic, whereas the white matter was relatively intact. It was supposed that these alterations were the result of a developmental disorder of the matrix, due to a toxaemia of pregnancy.

Case 2.—The mother had a similar toxaemia during the seventh month of her first pregnancy, when she was carrying the child I shall now discuss. This became worse during the last three weeks of pregnancy, necessitating its termination. The child was born in face presentation and in the beginning she was cyanotic. She cried for the first time when she was 19 days old. Thereafter there were no signs of any intellectual development. She did not fix objects with her eyes and did not react to people or stimuli, with the exception of music. She could not lift her head or trunk and a severe flexion contracture of both legs developed, necessitating orthopaedic measures. During the night she had screaming fits.

The skull was dolichocephalic and microcephalic. She was blind, with a nystagmus, but the optic discs were normal. There were spontaneous movements of the left arm only. The right arm was in extreme flexion contracture and displayed athetoid movements. Both legs were paralytic with exaggerated reflexes and a normal plantar response. During the examination she had small fits, with turning of the head and eyes to the left and jerking movements of all the limbs.

The cerebrospinal fluid was normal and other laboratory investigations showed no abnormalities. The Wassermann reaction was negative in the blood and C.S.F. of the patient and in the blood of both parents. It was impossible to make a good E.E.G. of the patient.

Necropsy Findings.—The child died suddenly at the age of 8 years and 9 months and two hours after death necropsy was performed. The weight of the brain was 810 g. The cerebellum was abnormally large as compared with the hemispheres. Blood vessels were normal and the venous sinuses were patent.

In the right hemisphere the gyri of the parietal and occipital lobes were small and firm, the frontal and temporal lobes being normal. The left hemisphere was much more affected than the right. The left frontal lobe was much smaller and the sclerogyria (ulegyria) reached rostrally as far as area 9, area 4 being small and tortuous as well. The brain substance of the left parietal and occipital lobes (especially area 19) was reduced to a thin sheet, but the left temporal lobe was relatively normal. If one compares the affected parts with the myelogenetic map of the cerebral cortex of Flechsig, no distinct correlation is found between these and the

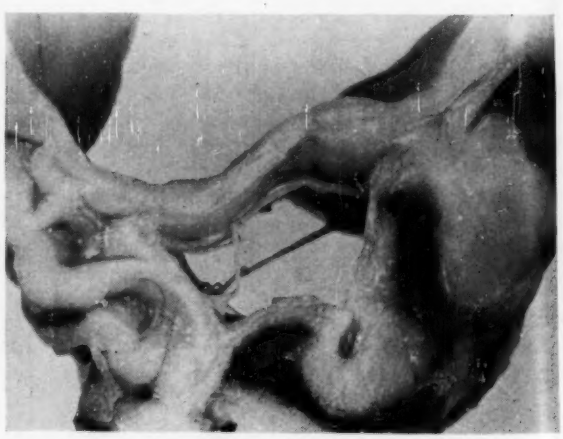


FIG. 8.—Cavitation of the white matter and enlarged ventricle.

FIG. 9

FIG. 10

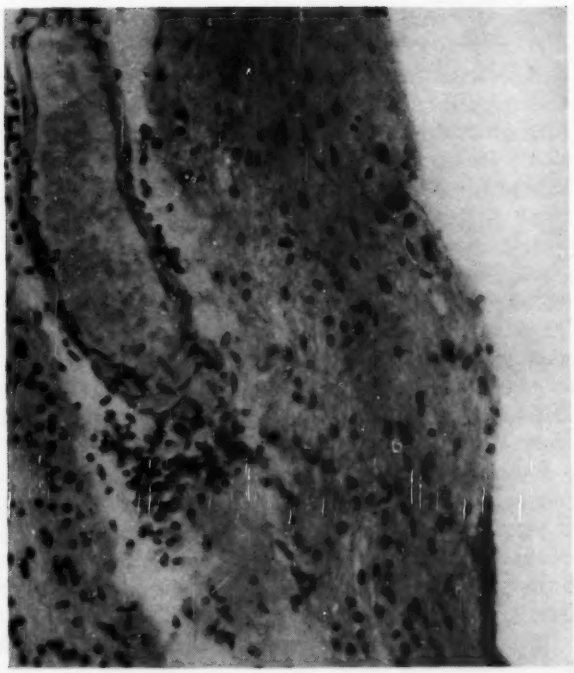


FIG. 11

FIG. 9.—Cortical convolution traversed by strips of fibrous glial tissue.

FIG. 10.—Subependymal gliosis.

Fig. 11.—Immature cells around a blood vessel.

period of myelogenesis. On transverse section of the hemispheres small cysts of the white substance of the altered parts were opened which contained a clear fluid (Fig. 8).

Microscopic Studies.—The leptomeninx was slightly thickened by an increase of connective tissue, while signs of inflammation were entirely lacking. Cysts were only found in the white matter. They developed by loosening of the pre-existing glial tissue, in which fat granule cells took no part. At the base of a fissure the " U " fibres degenerated primarily, contrary to what is found in diffuse sclerosis. The process of cavitation was especially found in places where the bottom of the fissure reached as far as the white matter, not covered by a layer of cortex. This phenomenon was interpreted as a sign of developmental disorder of fissuration. In the affected areas of the brain the glia seemed to have a tendency to proliferate. Immature cells were met with and amitotic division of cells was not uncommon. Moreover, binucleated cells were met with. The cortex was invaded by septa of fibrous glial tissue, coming from the underlying altered white matter (Fig. 9). The cortex was transformed into a dense glial tissue, without softening or cavitation. Fat granule cells were only found in small numbers in perivascular spaces. Also in this case an excess of subependymal cells was found in the region of the head of the caudate nucleus (Fig. 10), but also more peripherally (Fig. 11).

Discussion

A survey of the literature gives the impression that different causes give rise to cavitations which are morphologically the same. This is the reason why often one cause has been held responsible for all of them. Table II summarizes different aetiological possibilities which have been defended with more or less good arguments by the authors.

A primary softening of the brain parenchyma has usually been considered to be the cause of cavitation, followed secondarily by a glial proliferation. Therefore the genesis of multilocular encephalomalacia has often been related to the encephalitis interstitialis congenita of Virchow (1867) and this is the reason why blood vessel pathology has received so much attention in the past.

Others have looked for a connexion with neuropathological cases, in which cyst formation, not accompanied by large amounts of fat granule cells, is also found, such as porencephaly, Wilson's disease, or poliodystrophia cerebri progressiva infantilis.

It is rather difficult and perhaps impossible to give an explanation of the development of the cysts in these cases, as it evidently began before birth, whereas the examination took place 21 months (Case 1) and 105 months (Case 2) after birth. The earliest structural abnormalities are hidden or removed during the ripening process of the brain and the development of the histopathological processes themselves. Nevertheless I will present the following explanation.

TABLE II

AETIOLOGY OF ENCEPHALOMALACIA WITH OR WITHOUT CAVITATION IN THE NEWBORN

Brain Parenchyma
- *Disease* (degeneration) or *inflammation* (intra-uterine or post-natal): Henoch (1842), Heschl (1859), Roger (1866), Virchow (1867), Chiari (1880), Limbeck (1886), Salgo (1891), Hösel (1892), Birulja (1893), Henkel (1899), Schroeder (1899), Long (1907), Schmincke (1920), Ceelen (1920), Winkelman and Moore (1942), Ford (1952).
- *Intoxication:* Fischl (1899), Gohrbandt (1923), Diamond (1934) or *malnutrition:* Parrot (1868), Hayem (1868).
- *Mechanical injury: Intra-uterine:* Richter (1886), Seitz (1907).
  - *Birth trauma:* Cruveilhier (1832), Cotard (1868), von Limbeck (1886), von Monakow (1895), Siegmund (1923), Schütz (1925), Schwartz (1924), Dollinger (1927), Sternberg (1930), Rydberg (1932), Benda (1952).
  - *Extra-uterine:* Böettger (1869), Herter (1870), von Kahlden (1895), Dean (1898), Landouzy and Labbé (1899).
- *Congenital:* Heschl (1868), Diamond (1934), Stevenson and McGowan (1942).
  - *Retardation of development of white matter:* von Kahlden (1895).
  - *Insufficient glial reaction:* Spatz (1939), Lumsden (1950).
  - *Congenital hydrocephalus:* Schüle (1869), Mierzejewsky (1881).
- *Hereditary:* No data.

Blood Vessels (intra-uterine or post-natal)
- *Congenital aplasia:* Heschl (1859).
- *Ischaemic necrosis:* Kundrat (1882), de la Croix (1884), Lambl (1884), Otto (1885), Binswanger (1885), Petrina (1868).
- *Luetic degeneration of veins:* Pommer (1931).
- *Luetic endarteritis:* Takahashi (1921).
- *Spasm of blood vessels:* Dahlmann (1910), Meier (1912), Beneke (1914).
- *Thrombosis or embolism:* Heubner (1882), Kundrat (1882), Abercrombie (1887), Gowers (1888), Kreuser (1892), Beyer (1897), Wiglesworth (1897), Edgerley (1899), Scheffer (1900), Marburg and Casamajor (1944).
- *Thrombosis of superior longitudinal sinus:* Bailey and Hass (1937).

Meninges
- *Primary affection:* Schupfer (1901).

Skull
- *Maldevelopment of the base of the skull and the callosal body, resulting in atrophia of the white matter:* Richter (1886).
- *Aplasia of temporal bone and compression of brain:* Schaeffer (1896).

Case 1.—The family tree of this child makes it obvious that in this family a hereditary predisposition to degeneration of white matter existed. The " degeneration " in this case became manifest as a faulty development of the intermediate layer of His, from which the white matter is derived. I suppose that this was accompanied by a faulty development of the matrix. This assumption is based on the nodules of immature cells found in the neighbourhood of the ependyma and elsewhere. We have seen that this led to an excessive development of glia cells.

Subependymal nodules of cells were also found in similar cases by Schüle (1869), Obersteiner (1902), Dahlmann (1910), Ceelen (1920), Wohlwill (1921, *a* and *b*), Schmincke (1920), Siegmund (1923, *a* and *b*), Schwartz (1924), Jakob (1931), Diamond (1934). Fischl (1899), Ceelen (1920), and Schmincke (1920) thought that they were mesodermal (inflammatory) in nature, but His (1904), Ranke (1910 *a* and *b*), and Wohlwill (1921, *a* and *b*), proved their ectodermal origin. A second question was whether these

formations of cells were pathological at all and if so, whether they were a sign of retardation in development or of active proliferation caused by a detrimental agent. And thirdly the problem arises about the relation between these cells and the pathological process. A critical survey of this material was also given by Guillery (1923).

In my opinion the nests of immature cells found in Case 1 were centres of proliferation, furnishing cells for the cystic growing process. The same significance was given to these subependymal cell nodules by Gohrbandt (1923), who examined the brains of 130 newborn infants with various histopathological alterations. In his opinion remnants of the matrix would keep their tendency to proliferate even during the first months of life.

Very little is known of the pathology of the foetal nervous system, but Patten (1952, 1955) described an overgrowth of the neural tube in human embryos, ranging from 7·5 to 30 mm. Factors which regulate the proliferating processes of the brain in embryos were studied by Källèn (1955) who reported on the influence of the basal mesodermal plate of the skull on the cell division of the brain. In any case the causative mechanism of an early overgrowth of the neural tube is entirely different from a so-called "arrest of development".

Concerning Case 1, the question arises whether the glial proliferation started first in the matrix or whether the abnormal cell formation was the sequel of irritation of the matrix cells by some previous developmental abnormality of the white matter. Either possibility is difficult to prove, as only vestiges of the original malformation of the matrix and of the intermediate layer were left for us. However, both processes may have developed simultaneously.

Whatever the origin of the abnormal cells may be, the abnormality started rather late, as the general configuration of the brain was relatively normal.

We can only guess how the earliest (primordial) cysts arose during the abnormal development of the intermediate layer. There is no justification for a mechanical explanation, nor do the indifferent cells themselves form cysts, such as we see in ependymomas. We have to be content with the acceptance of a primary loss of tissue within an abnormal cell stratum resulting in cavity formation (see the hypothesis of Lumsden, 1950). This cell stratum, being abnormal, found no pattern of blood vessels correlated with its needs and it is possible that this contributed to the formation of the cysts, as the fluid within them is apparently provided by blood vessels. Moreover, we have to remember that a loosening of nervous tissue and cysts is found in a certain stage in normal embryos (Gruenwald, 1945). The mechanism by which this disintegration and such cysts develop is not yet understood.

The formation of the cavities continued after birth and we have seen how cavities developed after homogenization, hydropic degeneration, and softening. The presence of undifferentiated cells and cell divisions found in the neighbourhood, and especially the invasion of the cortex by fibrous glial tissue, makes it evident that the glia cells play an active role.

Degeneration and proliferation are, however, combined in this case and it is impossible to disentangle the two processes on purely morphological differences.

This process bears much resemblance to the cyst-like changes in bone or the growth of a congenital cystic liver or kidney. That the growing process is to be compared with a benign tumour is supported by the clinical progress.

This pathogenetic view may throw some light on otherwise unresolvable questions, such as the progress, the localization in neopallial structures, and the development of the malacia independently of the blood vessels, or around normal vessels, etc.

Case 2.—The second case differed in many respects from the first one. The mother had a toxaemia of pregnancy which might have been the cause of abnormal developmental processes within the brain. In any case the cerebellum was relatively very large, which may have been the cause of the birth in face presentation. Whether the brain was damaged during birth remains unanswered, but the head was not large, as birth took place before term. Moreover, in many cases of multilocular encephalomalacia in the literature (Jakob, 1931; Dahlmann, 1910; Meier, 1912; Edinger and Fischer, 1913; Negrin, Lepow, and Miller, 1952) birth was normal.

Signs of impaired cerebral functioning were evident immediately after birth, as in Case 1, but there was no clinical progress, and the patient died accidentally.

The cysts were less numerous than in Case 1 and the lesions were less extensive. Cysts were confined to the white matter and a correlation with the time of myelination was not apparent.

The cortex was transformed into a dense network of glia cells originating from the underlying altered white matter.

Also in this case immature cells were found in the neighbourhood of the ependyma and around blood vessels in the white matter, though in a smaller number than in Case 1. This might be explained by the greater age of the patient and by the fact that the disease was not rapidly progressive. However,

there was some progress as amitotic division of cells was met with. That the process was less active than in Case 1 was also evidenced by the fact that signs of softening, with the formation of fat granule cells, were less marked.

In this second case the toxaemia of the mother may have damaged the brain in a state in which remnants of the matrix of the neopallium had the ability to proliferate. The cell proliferation was combined with the formation of a dense network of glial fibres. These formed a capsule around relatively normal brain tissue, which underwent a process of softening and cavitation as described. Contrary to Case 1 the proliferating process stopped at an early stage so that the clinical signs were not progressive.

It is interesting to note that the toxaemia of the mother impaired histogenesis during intra-uterine life of both children in a different way. In the first child, which was described under the title " multilocular encephalomalacia ", the matrix of the neopallium was stimulated to proliferation leading to cavitation and scarring of some parts of the white matter and cortex. However, in the second child (poliodysplasia) a disordered histogenesis led to an under-development of both the nerve cells and the glial elements in all parts of the brain. Thus, contrary to Lumsden (1950) I deny the heredodegenerative character of both disorders and I see no relation with Wilson's disease, the condition described by Jakob and Creutzfeld.

Summary

Numerous cysts of different size and shape in both hemispheres of the brains of the newborn is a rare pathological condition. Such cases may be classified together on account of their gross morphology, but the cause is not always the same and the clinical features and the histological picture may differ as well.

The development of the pathological processes in two cases is described.

The first case, a child of 1 year and 9 months, was characterized as a familial, dysgenetic, progressive sclerosis of the hemispheres with cavity formation.

The second case was presented as an unprogressive, toxic, dysgenetic sclerosis of the hemispheres with cavity formation in a girl of 8 years and 9 months.

References

Abercrombie, J. (1887). *Brit. med. J.*, **1**, 1323.
Bailey, O. T., and Hass, G. M. (1937). *J. Pediat.*, **11**, 755.
Benda, C. E. (1952). *Developmental Disorders of Mentation and Cerebral Palsies.* Grune and Stratton, New York.
Beneke (1914). *Münch. med. Wschr.*, cited by Sternberg as 1914.
Beyer, E. (1897). *Neurol. Zbl.*, **16**, 631.
Biemond, A. (1954). *Rev. neurol. (Paris)*, **91**, 3.
Binswanger, O. (1885). *Virchows. Arch. path. Anat.*, **102**, 13.
Birulja, T. (1893). *Wjestink Psychiatrii i Neuropathologii*, 10.
Böettger (1869). *Allg. Z. Psychiat.*, **26**, 229.
Brocher, J. E. W. (1932). *Z. ges. Neurol. Psychiat.*, 142, 107.
Ceelen, W. (1920). *Virchows Arch. path. Anat.*, **227**, 152.
Chiari, H. (1880). *Jb. Kinderheilk.*, **15**, 330.
Cotard (1868). Thèse de Paris.
Croix, N. J. de la (1884). *Virchows Arch. path. Anat.*, 97, 307.
Cruveilhier, J. (1832). *Anatomie Pathologique du Corps Humain.* Tome I, Livraison 17. Bailliére, Paris.
Dahlmann, A. (1910). *Z. ges. Neurol. Psychiat.*, **3**, 223.
Dean, H. P. (1898). *Lancet*, **2**, 145.
Diamond, I. B. (1934). *Arch. Neurol. Psychiat. (Chicago)*, **31**, 1153.
Dollinger, A. (1927). *Ergebn. inn. Med. Kinderheilk.*, 31, 373.
Edgerley, S. (1899). *J. ment. Sci.*, **45**, 562.
Edinger, L., and Fischer, B. (1913). *Pflügers Arch. ges. Physiol.*, **152**, 535.
Fischl, R. (1899). *Jb. Kinderheilk.*, **49**, 58.
Ford, F. R. (1952). *Diseases of the Nervous System in Infancy, Childhood, and Adolescence*, 3rd ed., p. 363. Thomas, Springfield, Illinois.
Gohrbandt, E. (1923). *Virchows Arch. path. Anat.*, **247**, 374.
Gowers, W. R. (1888). *Lancet*, **1**, 709, 759.
Gruenwald, P. (1945). *J. Neuropath.*, **4**, 178.
Guillery, H., Jr. (1923). *Z. ges. Neurol. Psychiat.*, **84**, 205.
Hayem, G. (1868). *Études sur les diverses formes d'encéphalite*, p. 79. Delahaye, Paris.
Henkel, F. (1899). *Ann. allg. Krankenh. München*, 1896, p. 127.
Henoch, E. (1842). Wochenschrift für die gesammte Heilkunde, p. 657. ed. Casper, Berlin.
Herter (1870). *Drei Fälle von Encephalocele und ein Fall von Schädeldefect mit Porencephalie.* Inaug. Diss., Berlin.
Heschl, R. (1859). Vierteljahrschrift f.d. prakt. Heilk. (Prag.), **61**, 59.
Heubner (1882). *Berl. klin. Wschr.*, **19**, 737.
His, W. (1904). *Die Entwickelung des menschlichen Gehirns während der ersten Monate.* Hirzel, Leipzig.
Hösel, O. (1892). *Arch. Psychiat. Nervenkr.*, **24**, 452.
Jakob, A. (1931). *Dtsch. Z. Nervenheilk.*, **117-119**, 240.
Kahlden, C. von (1895). *Beitr. path. Anat.*, **18**, 231.
Källén, B. (1955). *Regulation of Proliferation Processes During Ontogenesis of the Brain.* Advance Abstracts International Meeting of Neurobiologists, p. 34. Groningen.
Kramer, W. (1953). *Acta psychiat. (Kbh.)*, **28**, 413.
Kreuser, H. (1892). *Allg. Z. Psychiat.*, **48**, 146.
Kundrat, H. (1882). *Die Porencephalie.* Leuschner and Lubensky, Graz.
Lambl, D. (1884). *Arch. Psychiat., Nervenkr.*, **15**, 45.
Landouzy and Labbé, M. (1899). *Presse méd.*, 7 (2), 93.
Limbeck, R. von (1886). *Z. Heilk. (Prag.)*, **7**, 87.
Lumsden, C. E. (1950). *J. Neuropath.*, **9**, 119.
Marburg, O., and Casamajor, L. (1944). *Arch. Neurol. Psychiat. (Chicago)*, **52**, 170.
Meier, E. (1912). *Jb. Kinderheilk.*, **76**, 552.
Mierzejewsky (1881). *Arch. neurol. (Paris)*, **1**, 353.
Monakow, C. von (1895). *Arch. Psych'at. Nervenkr.*, **27**, 406.
Negrin, J., Lepow, H., and Miller, B. (1952). *J. Neuropath.*, **11**, 62.
Obersteiner, H. (1902). *Arb. neurol. Inst. Univ. Wien*, **8**, 1.
Otto, R. (1885). *Arch. Psychiat. Nervenkr.*, **16**, 215.
Paltauf, R. (1901). *Wien. klin. Wschr.*, **14**, 1036.
Parrot, J. (1868). *Arch. Physiologie normale et pathologique*, **1**, 530.
Petrina (1868). *Prag. med. Wschr.*, 349.
Pommer, G. (1931). *Virchows Arch. path. Anat.*, **282**, 456.
Ranke, O. (1910a). *Beitr. path. Anat.*, **47**, 51.
—— (1910b). *Zbl. allg. Path. path. Anat.*, **21**, 386.
Richter, A. (1886). *Virchows Arch. path. Anat.*, **106**, 390.
Roger (1866). *Ueber die Porencephalie.* Inaug. Diss., Erlangen.
Rydberg, E. (1932). *Acta path. microbiol. scand.*, Suppl. 10.
Salgo (1891). *Bull. Soc. Méd. ment. Belg.*, 592.
Schaeffer (1896). *Virchows Arch. path. Anat.*, **145**, 481.
Scheffer, J. C. Th. (1900). *Psychiat. neurol. Bl. (Amst.)*, **4**, 37.
Schmincke, A. (1920). *Z. ges. Neurol. Psychiat.*, **60**, 290.
Schroeder (1899). *Allg. Z. Psychiat.*, **56**, 387.
Schüle, H. (1869). *Ibid.*, **26**, 300.
Schupfer, F. (1901). *Mschr. Psychiat. Neurol.*, **10**, 32.
Schütz, A. (1925). *Z. ges. Neurol. Psychiat.*, **94**, 639.
Schwartz, P. (1924). *Ibid.*, **90**, 265.
Seitz, L. (1907). *Arch. Gynäk.*, **83**, 701.
Siegmund, H. (1923a). *Münch. med. Wschr.*, **70**, 137.
—— (1923b). *Virchows Arch. path. Anat.*, **241**, 237.
Spatz, H. (1939). *Z. ges. Neurol. Psychiat.*, **167**, 301.
Sternberg, C. (1930). *Beitr. path. Anat.*, **84**, 521.
Stevenson, L. D., and McGowan, L. E. (1942). *Arch. Path. (Chicago)*, **34**, 286.
Takahashi, A. (1921). *Virchows Arch. path. Anat.*, **232**, 95.
Verhaart, W. J. C. (1936). *Z. ges. Neurol. Psychiat.*, **154**, 400.
Virchow, R. (1867). *Virchows Arch. path. Anat.*, **38**, 129.
Wiglesworth, J. (1897). *Brain*, **20**, 88.
Winkelman, N. W., and Moore, M. T. (1942). *Arch. Neurol. Psychiat. (Chicago)*, **48**, 54.
Wohlwill, F. (1921a). *Z. ges. Neurol. Psychiat.*, **68**, 384.
—— (1921b). *Ibid.*, **73**, 360.
Yakovlev, P. I., and Wadsworth, R. C. (1946). *J. Neuropath.*, **5**, 116, 169.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 217.

THE PATHOLOGICAL EFFECTS OF CEREBRAL ARTERIOGRAPHY

BY

T. CRAWFORD

From the Department of Pathology, St. George's Hospital Medical School, London

Cerebral arteriography is now carried out on a very large number of cases each year in the neurosurgical centres of the world. Usually this investigation is without harmful effect and the information gleaned commonly provides a precise diagnosis and leads to the institution of palliative or curative treatment. Nevertheless, there is inevitably some degree of damage to the arterial wall and in a very small proportion of cases harmful effects ensue. It seems important therefore that those who prescribe and carry out this procedure should be aware of the degree of damage commonly inflicted and of the occasional harmful effects which may follow. The method by which the arterial puncture wounds inflicted during arteriography heal "normally" has been described already (Crawford, 1956) and requires summarizing only briefly here. After some haemorrhage the track is filled by a fibrin plug. Endothelial cells proliferate and cover the central end of the plug by about the seventh day and thereafter the plug becomes organized by a dual mechanism from the lumen and from the adventitia similar to that seen in the organization of arterial mural thrombi (Crawford and Levene, 1952). By about the 28th day organization is complete and a fibrous scar marks the site of puncture. Over the succeeding months a few elastic and smooth muscle fibres develop in the scar but even at eight months there is no proper reconstitution of the media or of the elastic laminae (Fig. 1).

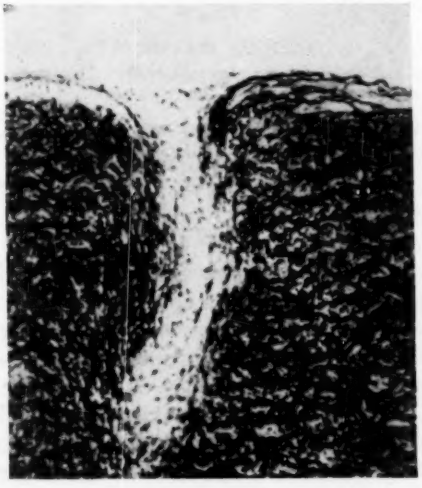


FIG. 1.—Site of arterial puncture made eight months before death. Elastic tissue has not regenerated. Weigert's elastic stain, ×65.

This "normal" healing process occurs in the great majority of needle-tracks but departure from the simple healing process may occur in a variety of ways and produce effects of varying significance. It is with these "abnormal" effects of arterial puncture that the present paper is concerned. The descriptions which follow are based on necropsy material from 75 subjects on whom arteriography had been carried out at intervals varying from two hours to eight months before death. This material has come from many different sources and has not been confined to the necropsies from a single neurosurgical unit.

Concealed Haemorrhage

There is always some haemorrhage from the arterial puncture wound. In most cases it leads to no more than staining of the carotid sheath for a distance of three or four centimetres above and below the puncture; but quite often the entire carotid sheath is distended with blood from the arch of the aorta to the base of the skull (Fig. 2) and occasionally the blood breaks out from the sheaths and spreads widely amongst the structures of the neck and mediastinum (Fig. 3).

It has been noticed that haemorrhage is usually minimal in young subjects and most marked in elderly hypertensives or when the vessel has been transfixed by the needle (or punctured repeatedly) with the infliction of two or more wounds (Fig. 4).

These haemorrhages are such a striking feature at necropsies on recently punctured cases that it is surprising to the pathologist to learn that significant symptoms rarely occur. Transient pain, tenderness, and dysphagia may be admitted on questioning. Persistent damage has not been seen in this study.

FIG. 2

FIG. 4

FIG. 3

FIG. 2.—Carotid sheath distended with blood. The arterial puncture site can be seen just below the bifurcation.

FIG. 3.—Extensive haemorrhage into the tissues of the neck and mediastinum after carotid arteriography in a hypertensive woman.

FIG. 4.—Twin needle tracks in the wall of a carotid artery. Weigert's elastic stain, ×25.

Abscess Formation

Pyogenic infection has not been found in any of the necropsy material: but in several of the cases coming to necropsy within a week of arteriography the arterial wall was found to be heavily infiltrated with polymorphs in the neighbourhood of the needle track while a few showed sterile abscess formation in the adventitia and sheath of the artery (Fig. 5). There can be little doubt that these inflammatory reactions and sterile abscesses are due to injection of contrast medium into the tissues of the arterial wall and sheath—an impression confirmed by the finding of numbers of foamy macrophages amongst the polymorphs. Although harmful effects of these reactions have not been recognized, damage to the important nerves in close anatomical relationship to the carotid arteries could well result, and the further complication of thrombosis is more likely when the vessel wall has been damaged by an intramural injection.

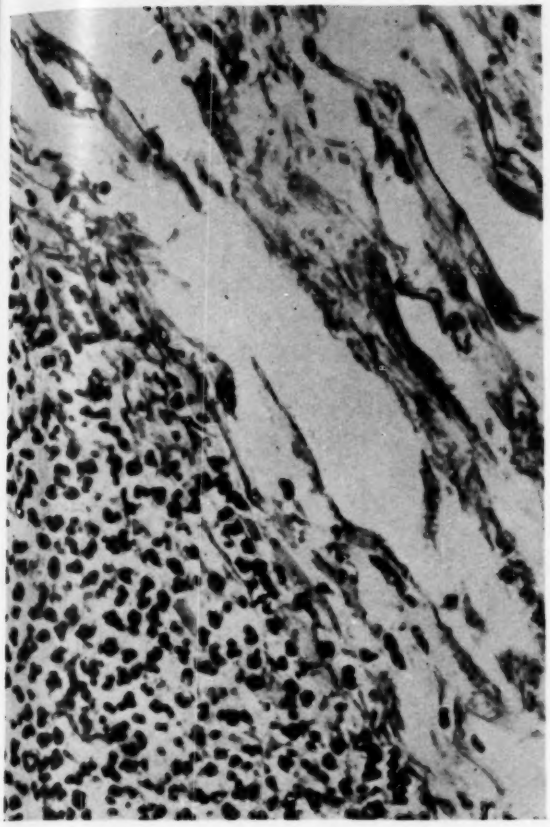


FIG. 5.—Sterile abscess in the carotid sheath. The arterial adventitia is seen above and to the left. Picro-Mallory, ×280.

Thrombosis

This is perhaps the most important complication of arterial puncture for it is important not only in its direct effects but also as the precursor of embolism.

Occlusive Thrombosis.—Occlusive thrombosis affecting both common carotid arteries has been found once. In both vessels rapidly formed thrombus extended up from the puncture as far as the bifurcation. The patient was an elderly hypertensive man with massive intracranial haemorrhage and it was impossible to distinguish the effects of the thrombosis on the course of the disease. Obstruction of one carotid artery has been found four times. The subjects were all over 55 years of age and there was advanced atherosclerosis in the affected arteries. Here again the possible effects of the arterial obstruction were obscured by the progress of the severe subarachnoid haemorrhages for the localization of which the arteriographies had been performed but in one patient dying on the third day after arteriography early softening was found in the hemisphere on the affected side.

Mural Thrombosis.—Mural thrombosis at the site of arterial puncture is a frequent finding—in fact, some minor degree of it is an almost constant occurrence. Usually it consists merely of slight lateral extensions of the fibrin plug in the needle track over the adjacent parts of the intima. A thrombus of this type will soon be incorporated into the intima and will ultimately lead to nothing more serious than a localized thickening of that layer. Sometimes, however, the mural thrombus assumes an irregularly pedunculated or polypoid form (Fig. 6). The danger of embolism is then self evident.

Cerebral Embolism

Embolism results from detachment of a mural thrombus which has formed at the site of the puncture. The effects of embolism will, of course, vary with the size and site of lodgment of the embolus and clinically they are likely to be obscured by, or mistaken for, the progress of the disease process. In the present series of cases there was one instance of fatal embolism of the basilar artery following vertebral arteriography. In five further cases necropsy revealed multiple cerebral infarcts though death was due to the progress of the primary disease. In these cases the site of carotid arteriography was the only likely site of origin for emboli. The patients

FIG. 6.—Mural thrombus with narrow attachment to the central end of the needle-track. Weigert's elastic stain, ×90.

were under investigation for subarachnoid haemorrhage. They showed rapid deterioration following arteriography, and necropsy confirmed that this was not due to recurrence of haemorrhage, though in each case the original damage from haemorrhage was of a grave nature.

Aneurysm Formation

Examination of the damaged vessel after recent arteriography punctures might lead one to anticipate that aneurysmal dilatation would be a frequent sequel but in fact trouble of this kind has not been encountered in the material studied. Two types of aneurysm—both of more pathological interest than clinical significance—have, however, been seen.

Traumatic False Aneurysm.—Two examples have been seen in which a small false aneurysm had developed through the needle track. One patient, a child aged 5 years, died 110 days after arteriography and at necropsy there was a berry-like nodule 1 cm. in diameter on the wall of the common carotid artery at the site of puncture. Serial sectioning showed it to be a false aneurysm lying outside the media but communicating with the lumen by an endothelialized track (Fig. 7). The second example was a similar lesion in an elderly woman who died on the 28th day after arteriography. In neither case did the aneurysm have any clinical effects.

FIG. 7.—Traumatic false aneurysm at the site of needle-puncture 110 days before death. Weigert's elastic stain, ×25.

Traumatic Dissecting Aneurysm.—Small dissecting aneurysms, consisting of blood-containing cavities in the substance of the media, have been seen to follow arterial puncture on nine occasions. These lesions have varied from 0·5 to 4·0 mm. in length and have caused the formation of a rather prominent ridge on the intimal surface with sometimes some overlying mural thrombus. A typical example is shown in Fig. 8. In two instances, in which death occurred on the 18th and 24th days respectively, the dissecting spaces in the vessel wall had become extensively endothelialized. It is interesting to note that these traumatic lesions occur at a similar depth in the media to that at which spontaneous dissecting aneurysms develop.

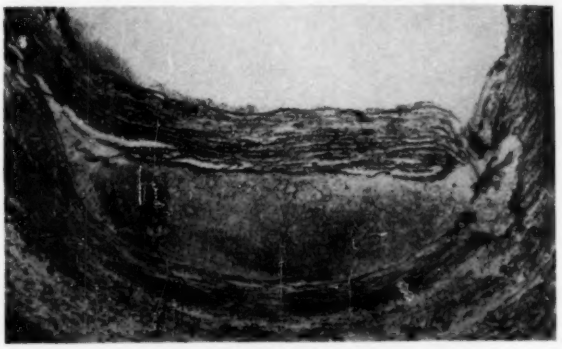


FIG. 8.—Traumatic dissecting aneurysm at the site of a needle puncture eight days before death. Weigert's elastic stain, ×30.

Discussion

It is important to appreciate that the lesions which have been described in the preceding sections occurred amongst many thousands of patients subjected to arteriography. No quantitative assessment of the frequency of each type of lesion can be made for many of the specimens were submitted to the author precisely because of some unusual occurrence. Nevertheless, it is possible to recognize certain factors which increase the liability to the development of complications. Advanced age, hypertension, and severe atherosclerosis are three linked factors which come into this category and which have been present in a high proportion of the cases in which thrombosis has occurred. On the technical side two further points emerge. In the first place, multiplicity of punctures, as when the vessel is transfixed, or when repeated punctures are made, greatly increases the amount of haemorrhage and the risk of thrombosis and embolism: and

secondly, puncture close to the point of bifurcation of the common carotid artery carries a greater risk of complications than when the artery is entered a few centimetres lower down. This is associated with the fact that the region of the bifurcation is commonly the site of advanced and perhaps calcified atheromatous plaques. When the needle penetrates such a plaque an irregular gash in the wall may result and form a suitable nidus for platelet and fibrin deposition.

It would be presumptious for the pathologist to offer unsolicited advice to the clinician and radiologist in a matter of this kind, but if advice were sought it might perhaps take the following form: reserve arteriography for the study of grave disease; beware the elderly arteriosclerotic hypertensive subject; avoid puncturing the immediate neighbourhood of the carotid bifurcation; puncture the vessel once only and do not transfix it; consider the possibility of embolism when fresh neurological manifestations follow the investigation.

Summary

Lesions resulting from arterial puncture have been studied in necropsy material from 75 patients dying at intervals varying from a few hours up to eight months after cerebral arteriography. The most serious ill effects observed have been carotid thrombosis and cerebral embolism. It has not been possible to assess the frequency of these rare misfortunes. They are more liable to occur in elderly hypertensive arteriosclerotic subjects.

I wish to thank the many pathologists who have contributed necropsy material to this study, especially Drs. W. Blackwood, D. Dexter, N. F. C. Gowing, J. Guthrie, R. Pearce, and R. D. Teare. Thanks are also due to the clinicians who have placed their records at my disposal.

The work has been supported by a grant towards technical assistance from the Research Fund of St. George's Hospital.

REFERENCES

Crawford, T. (1956). *J. Path. Bact.* In the press.
——, and Levene, C. I. (1952). *Ibid.*, **64**, 523.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 222.

ELECTROPHORESIS OF SERA IN MULTIPLE SCLEROSIS AND OTHER NEUROLOGICAL DISEASES

BY

ELIZABETH M. PRESS

From the S. A. Courtauld Institute of Biochemistry, Middlesex Hospital, London

It is a well established fact that in a large percentage of cases the cerebrospinal fluid gamma globulin is increased in multiple sclerosis but the serum gamma globulin is not raised. Changes in albumin and alpha and beta globulin concentrations have been reported by Bernsohn and Cochrane (1954) and by Volk, Saifer, Rabiner, and Oreskes (1955).

In the present investigations a comparison has been made of the serum proteins of 11 normal subjects, 28 patients with multiple sclerosis, and nine patients having other organic disease of the nervous system.

Method

Electrophoresis was performed on an Antweiler micro apparatus, using veronal buffer *p*H 8·6, I = 0·1, as described by Geissen, Schuler, and Schuster (1950). The normal controls ranged in age from 21 to 40 years, and the multiple sclerosis patients from 23 to 53 years, 13 being under 35 years. The duration of the disease was from a month to 15 years, and the average duration four and a half years. In 22 of the cases the disease was active.

Results

The mean values and standard deviations for the protein fractions in normal sera and sera of patients with multiple sclerosis are given in Table I. The

TABLE I

ELECTROPHORETIC ANALYSIS OF NORMAL SERA AND OF SERA IN MULTIPLE SCLEROSIS

	Albumin		Globulin					
			Alpha$_2$		Beta		Gamma	
	Mean %	S.D.	Mean %	S.D.	Mean %	S.D.	Mean %	S.D.
Normals (11)	63·4	2·7	7·7	1·5	13·0	2·6	15·9	2·7
Multiple sclerosis (28)	58·2	3·6	11·0	2·4	13·9	2·7	16·9	2·8

normal values are similar to those published by other workers (Bierring and Nielsen, 1952). Statistical analysis shows that for the multiple sclerosis patients the mean value of albumin concentration is significantly decreased and the alpha$_2$ globulin significantly increased ($P < 0.001$ in both cases). The mean concentrations for beta and gamma globulin, however, are not significantly different from the normal means ($P = 0.3$ in each case).

In order to determine whether there was any relationship between the concentration of serum alpha$_2$ globulin and the duration of the disease or the age of the patient, the multiple sclerosis patients were divided into two groups according to whether the duration was less than two years or more, and also according to age, over or under 35 years (Tables II and III). In both instances the differences

TABLE II

RELATIONSHIP BETWEEN ALPHA$_2$ GLOBULIN CONCENTRATION IN SERA IN MULTIPLE SCLEROSIS AND DURATION OF DISEASE

Duration of Disease	Mean Concentration % Total Protein	Standard Deviation	No. of Cases
Less than 2 years	11·3	2·2	11
More than 2 years	10·9	2·6	17

TABLE III

RELATIONSHIP BETWEEN ALPHA$_2$ GLOBULIN CONCENTRATION IN SERA IN MULTIPLE SCLEROSIS AND AGE OF PATIENTS

Age of Patient	Mean Concentration % Total Protein	Standard Deviation	No. of Cases
Under 35 years ..	10·8	2·4	13
Over 35 years ..	11·2	2·5	15

in the mean values of alpha$_2$ globulin were not significant ($P = 0.5$). The Lange gold curve was positive in the cerebrospinal fluid of 13 of the patients; the mean values of serum alpha$_2$ globulin of patients having positive and negative Lange gold reactions are shown in Table IV. There is no significant difference between these means ($P = 0.8$).

A comparison between the normals and the group of nine cases of organic disease of the nervous system (Table V) shows that the means of albumin, alpha$_2$, and beta globulins are significantly different

TABLE IV

RELATIONSHIP BETWEEN ALPHA$_2$ GLOBULIN CONCENTRATION IN SERA IN MULTIPLE SCLEROSIS AND CEREBROSPINAL FLUID LANGE GOLD TEST

Lange Gold Test	Mean Concentration % Total Protein	Standard Deviation	No. of Cases
Positive	11·1	2·7	13
Negative	10·9	2·2	15

TABLE V

ELECTROPHORETIC ANALYSIS OF NEUROLOGICAL SERA

Disease	Albumin (%)	Globulin		
		Alpha$_2$ (%)	Beta (%)	Gamma (%)
Tabes dorsalis	59	12	13	16
Chronic peripheral neuropathy	52	14	19	15
Chronic encephalomyeloradiculitis (inactive)	64	12	15	9
Polyneuritis	56	16	13	15
Intracranial aneurysm—ankylosing spondylitis	53	13	19	15
Haematomyelia	57	15	15	13
Brain-stem vascular lesion	55	10	15	20
Cervical spondylosis—pneumonia—angina pectoris	54	17	18	11
Paraplegia—diabetes mellitus—arteriosclerosis	50	12	22	16
Mean..	55·3	13·0	16·5	15·2
Standard deviation..	5·0	2·5	2·7	3·3
Normal Series Mean..	63·4	7·7	13·0	15·9
Standard deviation..	2·7	1·5	2·6	2·7

from the normal means ($P < 0.001$). The gamma globulin concentration is not significantly different from the normal value ($P = 0.5$).

Discussion

The disease was active in 22 of the multiple sclerosis patients, but only 12 of these had raised alpha$_2$ globulin concentration, *i.e.*, more than two standard deviations above the normal mean. Also, of the six patients in whom the disease was inactive, four had increased alpha$_2$ globulin concentration. There is, therefore, no correlation between the alpha$_2$ globulin concentration and the activity or duration of the disease, the age of the patient, or the results of the Lange gold reaction on the cerebrospinal fluid.

It is interesting to compare these results with those reported by Bernsohn and Cochrane (1954), who found the mean values of albumin decreased and alpha$_2$ increased in a series of 27 cases of multiple sclerosis. The duration of the disease is not stated, but the age of the patients ranged from 27 to 41 years. Also Volk and others (1955) reported a significant difference in the mean values of albumin, alpha$_2$, and beta globulin in a series of 43 cases of multiple sclerosis. In this series, however, the average duration of the disease was 18 years.

Increased alpha$_2$ globulin concentration has been reported in other pathological conditions. Longsworth, Shedlovsky, and MacInnes (1939) found increases in nephrosis and fevers, while Flynn (1954) reported increases in cases of high fever, tissue destruction, nephrotic syndrome, collagen disease, and malignant disease. The 28 patients with multiple sclerosis studied were all in-patients, and with one exception none were febrile or had other complications while in hospital. The only cases of infection were four patients with chronic tonsillitis and three with infected teeth. In each case electrophoresis was performed before the tonsillectomy or dental extraction. One patient had a history of recurrent thrombophlebitis and developed an attack at the site of the venepuncture carried out to obtain the specimen of blood for this study. It is evident, therefore, that the increased alpha$_2$ globulin and decreased albumin concentrations found in the sera of some of the multiple sclerosis patients are not due to fever, urinary, or other complications. These changes are not, however, specific for multiple sclerosis as they occur in other neurological diseases.

Summary

An increase in serum alpha$_2$ globulin and a decrease in albumin concentrations can occur in the early and later stages of multiple sclerosis. These changes cannot be correlated with the activity or duration of the disease, the age of the patient, or the Lange colloidal gold reaction on the cerebrospinal fluid and they are not specific for multiple sclerosis.

The author wishes to thank Dr. D. McAlpine for supplying the sera and the clinical data, and Professor Sir Charles Dodds and Dr. D. McAlpine for their advice and encouragement.

References

Bernsohn, J., and Cochrane, L. S. G. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 540.

Bierring, E., and Nielsen, E. (1952). *Scand. J. clin. Lab. invest.*, **4**, 281.

Flynn, F. V. (1954). *Proc. roy. Soc. Med.*, **47**, 827.

Geissen, W., Schuler, B., and Schuster, H. F. (1950). *Klin. Wschr.*, **28**, 751.

Longsworth, L. G., Shedlovsky, T., and MacInnes, D. A. (1939). *J. exp. Med.*, **70**, 399.

Volk, B. W., Saifer, A., Rabiner, A. M., and Oreskes, I. (1955). *A.M.A. Arch. Neurol. Psychiat.* **73**, 66.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 224.

BENIGN CONGENITAL MYOPATHY WITH MYASTHENIC FEATURES

BY

***JOHN N. WALTON, †NORMAN GESCHWIND, and ‡J. A. SIMPSON**

From the Neurological Research Unit and the Biochemical Department of the Institute of Neurology, the National Hospital, Queen Square, London

It has been increasingly apparent in recent years that in addition to cases which fall into recognizable categories of muscle disease, a number of less common disorders occur from time to time which do not correspond to the accepted descriptions. Some of these appear to be metabolic in origin and can be elucidated, at least in part, by modern methods of investigation (McArdle, 1951) while others seem to fall into a borderland of either myopathy or myasthenia gravis. A case of the latter type is described and discussed below.

Case History

R. M. (N. H. case 4838), a female telephonist, was born in 1919; her mother was well during pregnancy, labour was normal, and the baby thrived well during the neonatal period. She seemed normally active and lively and sat up at 7 months; at 9 months she tipped over her pram by jumping vigorously and sustained a cut chin but no other injury. Shortly after this episode her mother noticed that the limbs and body tended to flop limply when she was lifted and the head lolled as if she were totally unable to support it. The limbs were unusually flexible, like those of a rag doll, and she lay in her pram almost immobile, without kicking her legs or waving her arms. Nevertheless, at the age of a year she was able to crawl a short distance when put on the floor; her crawling improved steadily, although her limbs remained rather loose and "floppy". However, this was her only means of locomotion until she reached the age of 5 years, when she began to pull herself up with her arms and to walk around the furniture. When she was 5½ years old she was able to walk a few paces unaided and the limbs, though somewhat weak, were not so loose. The patient's mother suggested that at this age she was very little stronger but had learned to overcome her weakness. At the age of 7 she was able to go to a school for disabled children and could walk about 20 yards, but would then have to rest for about a minute in order to regain her strength. She always tended to tire throughout the day and was much weaker in the evening than on waking. She had particular difficulty in climbing stairs or in rising from a low chair and showed a considerable tendency to trip and fall, after which she would find it difficult to get up again. Apart from her muscular disability the patient developed normally; the menarche occurred at 13 years and she had menstruated normally since.

As the patient grew older she was gradually able to extend her activities, although her muscular weakness was virtually unchanged. She attempted numerous occupations and finally worked (from 1948) for two years as a telephonist, but was compelled to give up this post because of her muscular disability; since 1950 she had helped her mother in the home. The patient had two sisters, one older and one younger than herself, both of whom were well, and there was no history of muscular disease in the family.

The patient was first admitted to the National Hospital in 1941 under the care of Dr. E. A. Carmichael, when generalized muscular hypotonia of moderate degree and diffuse atrophy of proximal limb muscles were discovered. She showed an accentuated lumbar lordosis and tended to waddle when she walked. There was also bilateral ptosis and weakness of the upper facial musculature. A diagnosis of atypical amyotonia congenita was made. She was readmitted on several occasions during the ensuing years, when her symptoms and physical signs were virtually unchanged. In 1944 she was seen by Dr. Gordon Holmes, who suggested that she was suffering from an unidentified defect of muscle metabolism. In 1948 Sir Charles Symonds could demonstrate no myasthenic tiring of the eyelids, although there was pathological fatiguability of the deltoids; he agreed that the patient was suffering from an unusual metabolic disorder of muscle. On at least three occasions the effect of an intramuscular injection of 1·5 mg. prostigmine was tested. Each time the drug made the patient feel "queer" and dizzy, but nevertheless it produced some subjective improvement in muscular power, though there was little objective change. Twice the improvement in strength appeared to persist for two or three days after the injection and the drug was given by mouth in a dosage of up to 90 mg. daily. On each occasion there was a marked subjective improvement which, however, passed off after between one and two weeks and the treatment was discontinued. A similar improvement appeared to follow ephedrine, gr. ½, three times daily; the effect of

*King's College (Newcastle) Travelling Fellow in Medicine; aided by a grant from the Muscular Dystrophy Associations of America, Inc.

†Research Fellow, National Institutes of Health, U.S. Public Health Service, 1953-55.

‡Clinical Research Fellow of the Medical Research Council.

FIG. 1.—The bilateral ptosis and moderate atrophy of the shoulder girdle and arm muscles (particularly on the right side) are seen.

this drug was, in the patient's view, sustained, and she had been taking it continuously for several years. In 1952 the patient was admitted to the Clinical Research Unit at Guy's Hospital and was investigated by Dr. B. McArdle; the results of these studies are given below. At that time she seemed to show doubtful improvement on treatment with oral potassium (dosage 1 g. KCl t.d.s.) and had continued to take this remedy, as well as ephedrine, until she returned to the National Hospital in 1955. Assessment of therapeutic results in this patient was always difficult as she was a suggestible, nervous individual, who suffered numerous episodes of emotional instability, exaggerated by periods of conflict with her mother.

On readmission under the care of Dr. Carmichael on May 6, 1955, the patient's symptoms were virtually unchanged from those she had expressed on her previous admissions, save for the fact that she had experienced occasional dysphagia when tired. However, she was still able to do housework and to walk considerable distances (with many rest periods). She felt that the muscles of her legs seemed to " let her down " less often than they had done some years before, but there had been no striking change in the condition of the limbs for many years.

On examination (Fig. 1) the patient was thin and slightly built and walked with a distinct waddle and with a considerable increase in the lumbar lordosis. There was bilateral ptosis, with impaired ocular movement upwards, but not laterally or downwards; the ocular axes were parallel throughout and there was no diplopia. Both orbiculares oculi were strikingly weak, but the lower facial muscles, masseters, and temporales were strong. Palatal and pharyngeal movements were normal and the tongue showed no atrophy or fasciculation. The patient had a curiously long " swan-like " neck, but the sternomastoids were large and powerful as were the posterior cervical muscles; because of the ptosis she tended to hold her head backwards. There was undoubtedly atrophy of the sacrospinalis and other posterior spinal muscles, but those of the abdominal wall were good. The limbs were generally thin, particularly proximally, and there seemed to be a general moderate atrophy, with considerable weakness, of all girdle and proximal muscles in the upper and lower limbs. The extensors of the wrist and fingers were also weak; the finger flexors were stronger but, nevertheless, considerably weaker than would have been expected in a normal individual of the patient's age. In the lower limbs the anterior tibial and peroneal groups showed the same atrophy and weakness as the proximal muscles, although the calf muscles were more powerful. All deep tendon reflexes were present, though depressed, and direct muscle excitability was normal; the abdominal reflexes were brisk, the plantar responses flexor. The secondary sexual characteristics were normally developed and there was no abnormality to be detected on examination of the chest, abdomen, and cardiovascular system.

Electrodiagnosis.—In 1948, an intensity-duration curve from the right deltoid was normal; Dr. W. A. Cobb recorded an electromyogram from the same muscle, using a concentric needle electrode. He reported that there was no spontaneous activity and on voluntary contraction the motor unit action potentials were normal in amplitude and duration. In June, 1948, Dr. P. Merton found no decrement in the amplitude of a muscle action potential recorded with a surface electrode on the hypothenar eminence, on supra-maximal stimulation of the ulnar nerve at 3 per second.

Muscle Biopsy.—A specimen of muscle was removed from the right deltoid in 1950. There was no increase in perimysial connective tissue nor was there any accumulation of fat between the fibres. Some of the muscle fibres were slightly enlarged, measuring 85 μ in diameter, while very occasional atrophic fibres were seen. In a few fibres sarcolemmal nuclei had migrated into the substance of the fibre and one or two short chains of nuclei, subsarcolemmal in position, were seen. No segmental necrosis of fibres was evident and there was no cellular infiltration or evidence of muscle fibre regeneration. A number of nerve filaments were present in the section and appeared to be normal; two muscle spindles of normal appearance were also observed. Hence the histological changes were minimal. Although perhaps compatible with a mild myopathic disorder they were

much less than would have been expected considering the length of history and the comparative severity of the patient's weakness.

Dr. J. N. Cumings reported that the potassium content of the muscle was 1·1 g. % by dry weight, a normal figure.

Metabolic Studies.—Studies carried out in June, 1948, by Dr. J. N. Cumings yielded the following results:—

CREATINE AND CREATININE EXCRETION

Day	Urinary Volume (ml.)	Creatinine (g.)	Creatine (g.)	Inorganic Phosphate (g.)
1	900	0·73	0·18	0·51
2	820	0·84	0·27	0·53
3	940	0·86	0·12	0·41
4	763	0·79	0·16	0·40
5	570	0·75	0·04	0·51
6	940	0·87	0·08	0·56

Ephedrine medication and all other medicinal treatment was discontinued from the third day of this test; a creatine tolerance test was performed on the fourth day and gave results as follows :—

Creatine Tolerance Test.—Urinary and blood estimations were carried out at the stated times before and after the oral ingestion of 1 g. of creatine.

RESULTS IN URINE

Time	Volume (ml.)	Creatinine (g.)	Creatine (g.)	Inorganic Phosphate (g.)
Fasting	35	0·07	0·01	0·03
1 hour	57	0·05	0·05	0·02
2½ hours	121	0·10	0·04	0·03

RESULTS IN BLOOD

Time	Creatinine (mg. %)	Creatine (mg. %)	Inorganic Phosphate (mg. %)	Potassium (mg. %)
Fasting	1·0	0·38	4·3	19·4
1 hour	1·12	1·63	4·7	20·0
2½ hours	1·25	0·87	4·7	22·5

Response to Insulin and Glucose.—The patient was given 100 g. glucose by mouth and 25 units of insulin subcutaneously. Before the experiment was begun the serum potassium level was 20·0 mg./100 ml., the serum inorganic phosphate level 4·5 mg./100 ml., and the blood sugar level 100 mg./100 ml. Thirty minutes after the injection, the serum potassium level was 18·3 mg./100ml., the inorganic phosphate level was unchanged, and the blood sugar level was 168 mg./100 ml.

Dr. Cumings remarked that the urinary creatine was low and almost absent when the patient was taking no drugs, while the creatine tolerance and the potassium response to insulin and glucose were all normal.

Metabolic Activity of Forearm Muscles.—In January, 1952, the following studies were carried out by Dr. B. McArdle in the Clinical Research Unit at Guy's Hospital, London. The patient had received no drugs for about a week before the test. Blood was taken from the left antecubital vein before the test and again following the release of an occluding cuff after a period of ischaemic work by the forearm muscles. The work consisted in raising and lowering (56 pulls) a 5 kg. weight by means of a gripping movement on an ergometer. A wrist cuff inflated to 200 mm. Hg ensured that blood taken from the antecubital vein came only from the forearm muscles. The results of this test were as follows :—

Time	Blood Pyruvate (mg. %)	Blood Lactate (mg. %)	Serum Potassium (mg. %)	Serum Sodium (mg. %)	Serum Magnesium (mg. %)	Serum Inorganic Phosphate (mg. %)
Before	0·63	6·0	15·2	325	2·23	3·57
30 sec. after release of cuff	1·26	31·3	16·4	340	2·50	3·67
2 min. after release of cuff	0·91	29·4	15·6	—	—	—
6 min. after release of cuff	1·13	24·2	14·8	328	—	3·28
10 min. after release of cuff	1·01	16·3	14·7	330	—	—
20 min. after release of cuff	0·86	12·7	14·5	329	—	3·18

Dr. McArdle remarked that all of these results were within normal limits.

Other Investigations.—Haemoglobin was 100% (14·8 g./100 ml.); W. B. C. 4,000/c.mm. (63% polymorphonuclears, 31% lymphocytes).

The E. S. R. was 8 mm. in one hour (Westergren). The Wassermann and Kahn reactions were negative.

The serum protein-bound iodine was 3γ %. The total serum proteins were 7·9 g./100 ml. (albumin 4·4, globulin 3·5).

A radiograph of the chest showed a slight dorsal scoliosis, convex to the right. The lung fields and heart were normal and the thymus did not appear to be enlarged. An electrocardiogram was normal, and a basal metabolic rate was minus 11%. The urinary 17-ketosteroid excretion was 4·9 mg. in 24 hours.

Discussion and Experiments

It was clear from the information recorded that this patient fitted no clearly recognizable form of muscle disease as previously described. The non-progressive nature of the disease and the diffuse rather than selective distribution of muscular wasting and weakness made it apparent that she was not suffering from any of the common categories of muscular dystrophy. Furthermore, the pathological changes in the muscle were far less than would have been expected in a long-standing muscular dystrophy or polymyositis. She showed many characteristics reminiscent of the benign congenital myopathy or myopathic form of amyotonia congenita as described by Batten (1910) and by Aldren Turner (1940, 1949). Because of the general reduction in size of the skeletal muscles, the resemblance to Krabbe's (1946) "congenital universal muscular hypoplasia" was even more striking, since in Turner's cases the muscular wasting and weakness affected selectively the proximal muscles of the limbs and the face was not

involved. Despite these discrepancies, the results of a recent follow-up of cases of amyotonia congenita by one of us (Walton, 1956) have suggested that the disorders described by Krabbe and Turner may be the same. However, in this case there were additional unusual features: the variability of her weakness, the fatiguability, which had been a consistent feature, and the apparent response to ephedrine, suggested that there might be some defect in neuromuscular transmission akin to that seen in myasthenia gravis. It was evident that the patient was not suffering from the latter disease, in view of the diffuse muscular wasting and the failure to show a sustained response to prostigmine therapy. Rowland (1955) has recently described a number of patients who appeared to be suffering from myasthenia gravis but who showed either a very variable response to prostigmine or none at all. However, from his descriptions it seems likely that some of his cases were examples of polymyositis, a condition which may show temporary improvement with this drug (Eaton, 1954). It is clear from the clinical and pathological findings that our case was not suffering from polymyositis. An alternative possibility seemed to be that she was suffering from an unidentified disorder of muscle metabolism, although Dr. McArdle's results indicated that there was no serious defect in carbohydrate breakdown and utilization in the muscle.

In view of the apparent improvement which the patient had shown on potassium therapy it was decided to investigate the effect upon her muscular power of alterations in the serum potassium level. It was recognized that her symptoms were not like those of familial periodic paralysis, nor were they characteristic of those noted in chronic potassium deficiency (as in potassium-losing nephritis). It was also appreciated that the serum potassium level does not necessarily give a faithful indication of the intramuscular concentration of this ion. Nevertheless, since potassium is recognized to be one of the most freely diffusible ions, it was felt that if the patient's condition were due to a deficiency of intramuscular potassium, she would become significantly weaker if the serum potassium level were lowered. Another possibility seemed to be that she might have some anomaly whereby her muscles required a higher than normal concentration of potassium in order to function properly. In this case, too, a fall in extracellular potassium would increase her weakness.

It was also decided to repeat the electromyogram and to study the effects upon the muscle action potential of repetitive nerve stimulation, first under normal conditions and secondly after increasing doses of intravenous decamethonium iodide. Harvey and Masland (1941) found that in patients with myasthenia gravis, if the muscle action potential was recorded from the skin overlying a weak muscle during repetitive supramaximal stimulation of its nerve of supply at a rate of 3 per second, the potential often showed a rapid decrease in amplitude. This was suggested as a diagnostic test, and it has been conventional to take the recording from the hypothenar eminence during stimulation of the ulnar nerve at the elbow. If this muscle group is not clinically affected, however, another must be chosen. Recently, Churchill-Davidson and Richardson (1952) have shown that in the normal individual an intravenous injection of 2 mg. of decamethonium iodide will give a significant fall in amplitude of the motor unit potential recorded from the hypothenar eminence during stimulation of the ulnar nerve at a frequency of 10 per second. Patients with myasthenia gravis, however, in whom the hypothenar muscles were not weakened by the disease, were remarkably resistant to this drug and could often take 3 mg. or more without a significant decrement in the action potential.

Clearly it also seemed important in this patient to assess, under the conditions of a controlled experiment, the effect of ephedrine, prostigmine, tensilon, and potassium upon the muscular weakness. It was decided in addition to study the effects of intravenous caffeine and of calcium, in view of the direct stimulant effect which these substances appear to have upon the muscle fibre.

Before carrying out these experiments all treatment was stopped and the patient's muscular power was assessed three times daily by one of us, at 9.30 a.m., 1 p.m., and 5 p.m., in order to see whether there was any significant variation depending upon the time of day. The power of individual muscle groups was assessed clinically and strength of grip was measured with a spring dynamometer, the value recorded being taken as the average of three maximal grips with each of the two hands. It was discovered that the latter test gave a satisfactory indication of general muscular power. Another useful test was to measure the time for which both arms could be held out horizontally in front of the body with the patient sitting in bed; the end-point was taken at the time when one hand touched the bed-clothes. Using these methods it was found that after five days in hospital, with approximately the same amount of activity carried out each day, consistent values for strength of grip and for holding out the arms were obtained from day to day. Each day there was a consistent slight decrease in these readings as the day advanced; for this reason it

was decided to carry out all experiments at approximately the same time in the mornings. All chemical estimations were carried out by one of us (N. G.) using a standard technique. The assessments of muscular power were made by J. N. W. and electrodiagnostic tests were carried out by J. A. S.

Experiment I: Lowering of Serum Potassium Level.—On May 20, 1955, the patient was starved and 5 ml. of blood was taken from the right antecubital vein at 9 a.m.; the serum potassium level, as estimated with a flame photometer, was 4·4 mEq./litre (17·2 mg./100ml.). At 9.5 a.m. the patient was given 150 g. glucose orally and at 9.25 a.m. 25 units of insulin were given subcutaneously. At 10 a.m. muscular power was unaltered, but the serum potassium level was 4·1 mEq./litre (16·0 mg./100 ml.). Hence the fall in serum potassium level produced by this technique was inadequate.

On May 23, 1955, after a large breakfast, the serum potassium level was estimated at 9.10 a.m. to be 4·0 mEq./litre (15·6 mg./100 ml.). At 9.20 a.m., and again at 9.35 a.m. and 9.50 a.m. the patient was given 15 g. sodium bicarbonate in 2 oz. water. At 10.30 a.m. the patient felt somewhat tired and nauseated but there was no objective change in muscle power. At 1.15 p.m. the serum potassium level was 3·12 mEq./litre (12·2 mg./100 ml.) and 1 ml. of 1 in 1,000 adrenaline was administered subcutaneously. At 2 p.m. the serum potassium level had fallen to 3·0 mEq./litre (11·7 mg./100 ml.) but there was still no significant change in muscular power. This technique for lowering the serum potassium level will be reported in detail by one of us (N. G.) in a subsequent communication.

Experiment II: Electromyography and Effect of Intravenous Tensilon and Ephedrine.—On May 24, 1955, the electromyogram from the right deltoid muscle was recorded at 9.30 a.m., using a concentric needle electrode. There was no spontaneous activity; on voluntary contraction the interference pattern was sustained but contained an undoubted excess of polyphasic and short-duration potentials. After sustained abduction of the arm for 90 seconds, with the needle *in situ*, the proportion of short-duration and polyphasic potentials showed a significant increase. After assessment of voluntary power, 20 mg. " tensilon " was injected intravenously at 10 a.m. The patient immediately felt faint and dizzy and there was no increase in voluntary power, while the electromyogram was unchanged. At 10.50 a.m. ephedrine hydrochloride, gr. ½, was given intravenously; the patient immediately felt stronger, and voluntary power, as assessed with the dynamometer and by holding out the arms, increased to a level higher than any recorded since admission to hospital. The electromyogram now showed fewer polyphasic and short-duration potentials. The patient was unaware of the constitution of any of the injections she received.

Experiment III: Supramaximal Stimulation of Ulnar Nerve before and after Injection of Decamethonium Iodide.—On June 4, 1955, a surface electrode was applied to the left hypothenar eminence (with the indifferent electrode on the fifth finger), and at 10 a.m. recording of the action potential produced by supramaximal stimulation of the left ulnar nerve at the elbow was begun. With a stimulation frequency of 2 per second there was no significant decrease in amplitude of the motor unit potential over a 10-minute period. Stimulation was then discontinued but was restarted at 10.20 a.m. At 10.38 a.m. 1 mg. decamethonium iodide was injected over a two-minute period. Immediately the patient felt faint and dizzy (as after " tensilon "); her ptosis increased considerably and she developed diplopia, but the action potential of the hypothenar muscles was unchanged. At 10.44 a.m. and at 10.49 a.m. two further injections, each of 0·5 mg., were given; the patient felt subjectively weaker but there was no change in the action potential. A further injection of 0·5 mg. was given at 10.54 a.m. (total 2·5 mg.); at 10.59 the action potential showed a 13% decrease in amplitude; the patient felt weaker, was apprehensive, and refused to have further injections. The original amplitude of the action potential was restored by 11.25 a.m. With this dose of decamethonium, the action potential of a normal subject would decrease in amplitude by more than 50%. The results of this experiment are recorded graphically in Fig. 2, using the same ordinates as those utilized by Churchill-Davidson and Richardson (1952).

Experiment IV: Therapeutic Trials.—Five substances

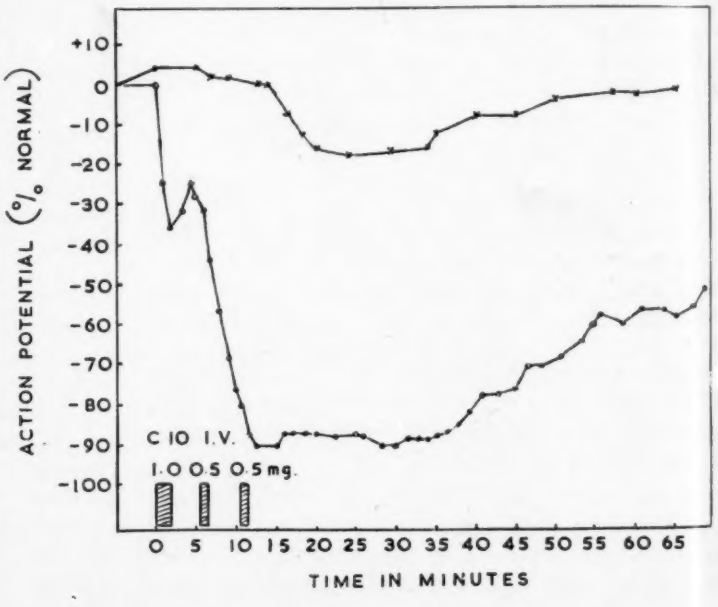


FIG. 2.—Effect of decamethonium on the action potential of abductor digiti minimi during supramaximal ulnar nerve stimulation in R.M. (upper curve) and in a control subject (lower curve).

were used, namely, ephedrine, calcium, potassium, caffeine, and prostigmine.

Ephedrine.—For a period of seven days from May 25, 1955, the patient was given tablets four times daily; for a part of this time the tablets were ephedrine hydrochloride (gr. ¼), and for the remainder nicotinamide 25 mg. (which looked identical). This trial was designed by J. A. S. so that neither the observer testing muscular power (J. N. W.), the patient, nor the ward nurses were aware which tablet was being given at any one time, nor when the treatment was changed. At the end of this period it was clear that during the three-day period of treatment with ephedrine the patient was both subjectively and objectively stronger than when she was receiving nicotinamide.

Calcium.—On successive days the patient received an intravenous infusion of 500 ml. of fluid over a two-hour period. One of these infusions consisted of 500 mg. of calcium (as the gluconate) in normal saline while the other was saline alone. The observer concerned with the measurement of the patient's muscular power was not aware which infusion was being administered. After each infusion the patient claimed to be considerably stronger and showed a moderate increase in power as recorded dynamometrically and by holding the arms outstretched.

Potassium.—Over a seven-day period, from June 5, 1955, the patient was given four times a day 1 oz. of an orange-flavoured preparation. For a part of this time the preparation contained 2 g. potassium citrate in each ounce and for the remainder sodium citrate. As with the trial of ephedrine neither the patient nor the observer was aware which remedy was being given at any one time nor when the change-over occurred. Throughout this period the patient's condition remained unchanged; neither substance produced a significant change in muscular power.

Caffeine.—On June 12, 1955, the patient received three intravenous injections of comparable volume and appearance at intervals of one hour. One was caffeine sodium benzoate, 0·5 g., another ephedrine hydrochloride, gr. ¼, and the other sterile saline. The injections were given by J. A. S. and neither the patient nor the clinical examiner (J. N. W.) was aware which injection was being given. It was discovered that the injection of saline had no effect, but both the ephedrine and the caffeine produced a distinct subjective and objective improvement in muscular strength of comparable degree.

Prostigmine.—On June 13, 1955, it was decided to study the effects of long-term oral prostigmine therapy, despite the fact that this treatment had proved ineffective in the past. Accordingly therapy with 15 mg. tablets of prostigmine four times daily was instituted, but was changed, at a time unknown to the patient and observer, to an inert tablet of identical appearance. This trial was continued over a five-day period. There was no doubt that both subjectively and objectively the patient was considerably stronger while on prostigmine. Indeed, she recorded higher dynamometer readings and was able to hold out her arms longer than at any time since her admission to hospital. During the next five days prostigmine therapy was alternated with pyridostigmine in equivalent dosage, but there was little difference in the effect of the two remedies, although overall improvement was maintained.

Subsequent Progress.—As a result of the findings in the experiments outlined above it was decided to give the patient combined treatment with prostigmine, one tablet of 15 mg., four times daily, and ephedrine, one tablet of gr. ¼, also four times a day. For three days the improvement in the patient's strength was sustained: she moved about the ward more easily, could lift objects of considerable weight, and climbed three flights of stairs relatively briskly. Unfortunately she then developed follicular tonsillitis with a high fever and was compelled to take to her bed. This infection resolved within a few days but left the patient depressed, tearful and weak, though no weaker than she had been on admission. She asked to be discharged, feeling that she would pick up more quickly at home; she therefore left hospital, taking both ephedrine and prostigmine, on June 23, 1955. On discharge, physical examination revealed no significant change from her state on admission.

The patient was readmitted to hospital on August 9, 1955. After returning home she had improved quickly and soon felt that her strength had returned to what it was after beginning combined prostigmine and ephedrine therapy in hospital. This improvement continued for three weeks but then she began to feel unaccountably weaker. Although she had experienced some fluctuation in her muscular strength as a result of emotional disturbances, the present deterioration was quite different, being steadily progressive. In addition, she became short of breath and could no longer lie down in bed at night, or walk more than a few paces because of dyspnoea. On examination on admission the patient was unable to walk more than a few paces with considerable effort and she was quite unable to negotiate stairs. Her resting pulse rate was 120 per minute, but the heart and chest showed no abnormality on examination. She was severely breathless, with very poor abdominal and thoracic movement and striking activity of the accessory muscles of respiration, including the sternomastoids and scaleni. Her ptosis and facial weakness had not increased since her previous admission but her strength of grip was strikingly weak and she was quite unable to lift her arms from the bed. Her vital capacity could not be measured as she said she was unable to blow into the machine. An electrocardiogram was normal but for the tachycardia. Although an accurate assessment of her physical state was made difficult by emotional factors, there was no doubt that she showed persistent tachycardia and severe weakness of limb, trunk, and respiratory muscles, like that seen in severe myasthenia gravis. Intravenous tensilon and intramuscular prostigmine therapy produced no improvement in her condition; indeed, she insisted that these remedies made her worse. After each, some muscular fasciculation was seen but there were no abdominal symptoms. Accordingly, all therapy was

discontinued and over the next two weeks there was a gradual improvement in her respiration and in the power of the limbs; her pulse rate returned to 80 per minute. The patient was finally discharged from hospital on September 16, 1955, receiving only ephedrine gr. ½ four times daily. Her condition was virtually the same as when she was first admitted in May, 1955.

Conclusions

There seems to be little doubt whatever that this patient was suffering from a relatively benign, probably congenital, non-progressive myopathy, showing certain features reminiscent of myasthenia gravis. Dr. McArdle's investigations revealed no apparent defect in carbohydrate metabolism, while we were unable to produce any evidence to indicate that alterations in serum potassium affected her muscular condition. Save for the " myasthenic " features, her condition corresponds closely to the " benign congenital myopathy " or myopathic form of amyotonia congenita described by Batten (1910) and Aldren Turner (1940, 1949). However, Turner did not describe any fatiguability or apparent response to ephedrine or prostigmine therapy in his cases, nor were these features seen in the other cases of this type which were reviewed recently by one of us (Walton, 1956). On the other hand, it is evident that this patient was not suffering from true myasthenia gravis, in view of the failure to respond to tensilon, as well as the atypical clinical picture. Nevertheless, it must be admitted that she showed a considerable resistance to decamethonium iodide, while the sustained improvement on ephedrine therapy and the temporary response to prostigmine were suggestive of the latter disease. The apparent increase in strength following an injection of caffeine sodium benzoate was of doubtful significance.

Of great interest was the striking increase in weakness, particularly of the respiratory muscles, after prostigmine therapy had been in progress for some weeks. The associated tachycardia was suggestive of vagal inhibition but it is difficult to see how moderate dosage of prostigmine, which would be expected to give a bradycardia, could produce this effect. It seems most probable that the weakness could be attributed to this drug, despite the absence of other side-effects, and that the temporary improvement, perhaps due to its anti-cholinesterase effect, was subsequently overcome by a persistent depolarizing effect which appeared to be cumulative. It is well recognized that even patients with myasthenia gravis may become weak as a result of excessive dosage of this drug (Rowland, Korengold, Jaffe, Berg, and Shy, 1955), but the dosage administered to our patient was only 60 mg. daily which could not be expected to produce such an effect in an individual with true myasthenia. It is also difficult to understand the action of ephedrine in this case. Unlike adrenaline, this drug does not cause glycogen breakdown, hyperglycaemia, or a fall in the serum potassium level. We may ask whether its effect is unrelated to the energy metabolism of muscle and whether it may have a direct effect upon the muscle membrane or perhaps at the motor end-plate. We have no evidence which could help in deciding this problem.

The paradoxical responses which this patient showed to ephedrine, prostigmine, decamethonium, and " tensilon " suggest that in her case there may be some hitherto unrecognized defect in the muscle fibre and/or its end-plate or membrane. We can think of no better description for her condition than " benign congenital myopathy with myasthenic features " while recognizing that we do not understand the essential nature of her disorder.

Although this patient, so far as we are aware, shows features which are unique, there is no doubt that other cases showing a resemblance to this clinical picture are seen from time to time. One of us (J. N. W.) in a previous communication (Walton and Nattrass, 1954) has referred to a number of cases of " myasthenic myopathy ". This term is probably unsatisfactory, as it could be taken to refer to the irreversible muscular weakness and atrophy which may develop in the limb or ocular muscles of certain long-standing cases of myasthenia gravis. One of us (J. A. S.) in a recent study of a large series of cases of the latter condition has come to feel that such changes occur in a not insignificant proportion of cases and may follow a recognizable pattern, particularly in the limb muscles. However, the three cases briefly referred to by Walton and Nattrass (1954) were not of this type; rather, they were individuals with a long-standing weakness and atrophy of girdle and limb muscles who yet showed a somewhat phasic course and a definite, though sometimes temporary, response to ephedrine and/or prostigmine. Similar patients with a clinical picture like a combination of muscular dystrophy and myasthenia gravis have been reported by Laruelle and Massion-Verniory (1937), by Jezkova and Sachs (1939) and by Hosotte (1951). Hosotte's case, however, may have been one of true myasthenia gravis with eventual amyotrophy. In none of the cases mentioned by Walton and Nattrass did the condition begin so soon after birth as in the patient described in the present report. It is of considerable interest that one of these patients, shortly to be reported by Griffin, Nattrass, and Pask (1956), was given increasing doses of prostigmine with apparent improvement in the power of the limbs, but

with eventual respiratory paralysis, necessitating management with intermittent positive-pressure respiration. He was subsequently subjected to thymectomy with dramatic improvement.

It must be concluded that there exist a number of obscure disorders falling into the borderland of both myopathy and myasthenia gravis, of which the present case is a striking example. We have at present, however, no information to indicate the the nature of the basic muscular defect in such individuals.

Summary

The case is reported of a woman who developed muscular weakness and hypotonia in the first year of life; she has shown subsequently persistent though non-progressive weakness, with moderate diffuse atrophy of the upper facial, trunk, and limb muscles. Her weakness has always become worse after exertion and she has had slight dysphagia but no diplopia.

Extensive metabolic, electrophysiological, and therapeutic experiments have revealed no defect in carbohydrate utilization or in potassium metabolism. She is more resistant to decamethonium iodide than the normal individual and shows improvement on ephedrine therapy but none following tensilon. Prostigmine produces definite improvement in muscular power, but if continued indefinitely in moderate dosage it appears to produce an increase in weakness, particularly of the respiratory muscles. A muscle biopsy revealed only slight, indefinite changes compatible with a myopathic disorder.

It is suggested that this condition falls into a borderland of myopathy and myasthenia and that it should be styled " benign congenital myopathy with myasthenic features ". It was not possible to determine the nature of the biochemical or other defect in the muscle fibre and/or its end-plate or membrane which was responsible for this patient's condition.

We wish to thank Dr. E. A. Carmichael for permission to report this case and for his encouragement and advice. We are also grateful to Dr. J. N. Cumings, Dr. B. McArdle, Dr. W. A. Cobb, and Dr. P. A. Merton for permission to quote their findings. Fig. 1 was prepared in the Department of Photography, the National Hospital, Queen Square, Fig. 2 in the Gardiner Institute of Medicine, University of Glasgow.

References

Batten, F. E. (1910). *Quart. J. Med.*, **3**, 313.
Churchill-Davidson, H. C., and Richardson, A. T. (1952). *Journal of Neurology, Neurosurgery and Psychiatry*, **15**, 129.
Eaton, L. M. (1954). *Neurology*, **4**, 245.
Griffin, S. G., Nattrass, F. J., and Pask, E. A. (1956). *Lancet*. In the press.
Harvey, A. M., and Masland, R. L. (1941). *Bull. Johns Hopk. Hosp.*, **68**, 81.
Hosotte, A. (1951). *Presse méd.*, **59**, 1146.
Jezkova, S., and Sachs, A. (1939). *Cas Lék. ces.*, **78**, 1354.
Krabbe, K. H. (1946). Kongenit generaliseret muskelaplasi, 338 meeting of the Danish Neurol. Soc.; case reported again by Brandt, S. (1950): *Werdnig-Hoffmann's Infantile Progressive Muscular Atrophy*, p. 264. Munksgaard, Copenhagen.
Laruelle, L., and Massion-Verniory, L. (1937). *J. belge. Neurol.*, **37**, 376.
McArdle, B. (1951). *Clin. Sci.*, **10**, 13.
Rowland, L. P. (1955). *Neurology*, **5**, 612.
——, Korengold, M.C., Jaffe, I. A., Berg, L., and Shy, G. M. (1955). *Ibid.*, **5**, 89.
Turner, J. W. A. (1940). *Brain*, **63**, 163.
—— (1949). *Ibid.*, **72**, 25.
Walton, J. N. (1956). *Lancet*, **1**, 1023.
——, and Nattrass, F. J. (1954). *Ibid.*, **77**, 169.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 232.

A CONTROLLED CLINICAL STUDY OF CHLORPROMAZINE AND RESERPINE IN CHRONIC SCHIZOPHRENIA

BY

MICHAEL SHEPHERD AND DAVID C. WATT

From the Professorial Unit, Maudsley Hospital and St. John's Hospital, Stone, Bucks.

Since their recent introduction into clinical practice, chlorpromazine and reserpine have been widely used in the treatment of the schizophrenias. Studies of schizophrenic patients treated with chlorpromazine have been published by Vaughan, Leiberman, and Cook (1955), Kinross-Wright (1955), Goldman (1955), Charatan (1954), Labhardt (1954) and Anton-Stephens (1954); treatment with reserpine has been reported by Foote (1955), Kline (1954), Hollister, Krieger, Kringel, and Roberts (1955), Kline and Stanley (1955), Tasher and Chermak (1955), Campden-Main and Wegielski (1955), Noce, Williams, and Rapaport (1955), Barsa and Kline (1955), and Glynn (1955). The claims made by these workers for the two drugs are not dissimilar, but only the study of Kinross-Wright attempts to compare their efficacy. It seemed desirable, therefore, to try and assess the relative merits of the drugs as accurately as possible.

Case Material and Method

For this trial, 24 of the most deteriorated and apathetic female schizophrenic patients in a county mental hospital (St. John's Hospital, Stone) were chosen. Their ages ranged from 27 to 52 years, with an average of 40·5 years. The age span on admission was 16 to 36 years, with an average age of 25·2 years. The length of stay in hospital varied from 7 to 29 years with a mean of 15·8 years; two patients only had been less than 10 years continuously in hospital.

A fairly uniform clinical picture was presented by this group of patients. Most were totally unoccupied, withdrawn and unsociable. They took no interest in their appearance or personal care and were incontinent of urine. Talk was so seriously disordered that an intelligible conversation was impossible. Many patients were mute; a few were noisy, interfering, hostile or destructive to clothing and property. The majority, however, were not predominantly over-active, aggressive or disturbing, but were characterized by long-standing apathy and inactivity.

The following case histories are representative:—

Case 9.—A telephone operator was admitted to the hospital in 1945, aged 18, after 12 months' illness. On admission she felt that her thoughts were being controlled and were not really her own; she had impulses to destroy property and hit other people. Later she became stuporose. She was mute, incontinent, paid no attention to her personal appearance, and had to be fed. She frequently struck other patients, tore up her own clothing and resisted attention. Treatment with barbiturate narcosis and E.C.T. had produced limited, short-lived improvements.

Case 10.—A factory machinist was admitted in 1948, aged 28 years. On admission she would speak only in whispers. She grimaced and smiled meaninglessly. She displayed no interest in people or things around her. Later she became mute. She improved with a short course of insulin coma treatment and was discharged three months after admission. Four months later she was re-admitted. She thought she was under the power of a hypnotist, was auditorily hallucinated, and showed inappropriate facial expressions. She was sometimes aggressive. She degenerated to a state in which she was mute, unoccupiable, indifferent to her surroundings and her appearance. She was incontinent unless taken to the lavatory regularly.

Case 22.—This patient was admitted in 1935, aged 23. She had three years previously been in a mental hospital for one year. On admission she was restless and violent; she indulged in outbursts of abusive language and sometimes of hilarious laughter. She talked incoherently. She slowly deteriorated, finally becoming mute, untidy, and incontinent. She did a little knitting but was otherwise unoccupied. About once a month she had an outburst of laughing or abusive shouting. She sometimes struck other patients for no reason; at other times she would tear her clothes.

The 24 patients were divided into three groups of eight (A, B, and C) by random selection. The experiment lasted for 18 weeks during which time each group of patients received each of three substances—reserpine (R), chlorpromazine (C), and placebo (P)—in different orders of administration. The original latin square design had to be modified for reasons described below. Dosage was necessarily empirical and was determined by experience and a study of the relevant literature. Chlorpromazine, 150 mg., was administered twice daily. The initial dose of reserpine was 5 mg. three times daily but owing to the frequency of toxic reactions this was reduced to

5 mg. reserpine twice daily later in the experiment. Two kinds of inert substance were employed, one indistinguishable in appearance and taste from reserpine, the other from chlorpromazine. Nobody but the ward doctor allocating the drugs and the dispenser knew which patients were receiving drugs and which patients were on placebo. A sealed list containing the nature of each substance prescribed was available, in case of need, *e.g.*, at night. The pulse rate and blood pressure readings were recorded regularly.

Weekly clinical assessments were carried out by one of us (D. C. W.) who was unaware of the nature of the individual prescriptions. At the end of each six-weekly period all patients were rated after an interview with the patient and a discussion with the nursing staff. This rating, though it simply indicated whether the patient had improved, deteriorated, or remained unchanged during the six weeks, was the expression of a complex judgment of nursing and medical factors. The rating 0 was used as a base-line index, signifying the patient's condition before the start of the treatment. Degrees of improvement in descending order were indicated by a+, b+, and c+, though equal degrees of improvement are not implied by these symbols. Conversely, a−, b−, and c− pointed to three progressive stages of deterioration. Examples from the cases already described above illustrate the use of the scale. It may be seen from these examples that the degrees of improvement corresponded approximately to different stages of rehabilitation, although the clinical symptoms remained in every case.

Case 9.—During the six weeks on chlorpromazine, she became more friendly and talkative; she ceased to be destructive and aggressive; she ate normal meals and was no longer incontinent; she was occupied a little and was clean and tidy; her facial expression and bearing were friendly and responsive. The possibility of discharge was considered. She was rated a+.

Case 10.—While having reserpine, she spoke more freely although the content of her talk was often nonsensical. She required less supervision for washing and dressing and went to the lavatory unaided; she did a little work spontaneously and appeared to enjoy television and other entertainments more. Transfer to another ward was considered. She was rated b+.

Case 22.—While having reserpine she became very restless: she ate ravenously and sometimes stole food from other patients. She could not be occupied. Nevertheless, she was incontinent less often and was no longer noisy, aggressive, or destructive. She was, therefore, much easier to nurse. She was rated c+.

In almost every case negative ratings were made on patients who were suffering from toxic effects of the drug which brought about a marked deterioration in behaviour. In these cases administration of the drug was discontinued or the dose reduced; in view of the period of "turbulence" described by Barsa and Kline (1955) the drug was not withdrawn until it was clear that the toxic effects were serious and were increasing. In the former instances the rating was made at the time when the drug was discontinued.

Results

The ratings made on the three groups after the administration of each substance are presented in Table I.

TABLE I
RATINGS ON ALL PATIENTS AFTER TREATMENT WITH RESERPINE, CHLORPROMAZINE, AND PLACEBO

A

Case Number	Period 1	Period 2	Period 3
	Placebo (r)	Reserpine	Chlorpromazine
1	0	a−	0 (T)*
2	0	c− (T)	a−
3	c+	a−	b+
4	b+	c−	a+
5	a−	b+ (T)	a+
6	0	c+	c+
7	0	0	0
8	b+	b+	b+

B

Case Number	Period 1	Period 2	Period 3
	Placebo	Chlorpromazine	Reserpine
9	0	a+	a+
10	0	a+	b+
11	0	c+	b−
12	c+	a−	a+
13	0	0	b− (T)
14	b+	b+ (T)	c− (T)
15	0	0	c+
16	c+	b+	c− (T)

C

Case Number	Period 1	Period 2	Period 3
	Chlorpromazine	Placebo	Reserpine
17	b−	b−	b−
18	a−	a−	b+
19	a+	b+	a− (T)
20	b+	b+	c+
21	0	c+	0
22	b+	a−	c+ (T)
23	a+	a+	a+
24	c+	b+	c+ (T)

* T = toxic reaction.

A word of explanation must be offered about the sequence of drug administration in these tables. The original sequences, chosen to conform with a latin square design, had to be modified because of an administrative error which reduced the dose of reserpine in the first period from 15 mg. to 0·75 mg. daily in group A. This quantity of reserpine (here designated r) was regarded as resembling more an inert substance than the drug in the treatment of such severely ill patients and it was thought advisable to include chlorpromazine and reserpine in full dosage in the remaining periods. A rearrangement of the sequence of administration therefore became necessary.

If the patient's condition is assumed to rate as 0 at the start of each six-weekly period, the ratings

made at the end of each period can be used to assess whether the patients had improved (a plus rating), became worse (a minus rating) or remained unchanged after the administration of each of the three substances. Table II relates these changes in the clinical condition to the three substances.

TABLE II

CLINICAL RESPONSE TO ALL DRUGS ASSESSED BY RATINGS AND COMPARED WITH PRE-TREATMENT CONDITION

Drug Employed	Responses		
	Unchanged	Improved	Worse
Chlorpromazine	5	15	4
Reserpine	2	12	10
Placebo	9	11	4

It is apparent that the responses differ, though not significantly ($\chi^2 = 9{\cdot}46$; d.f. $= 4$; $0{\cdot}1 > P > 0{\cdot}05$) and that by this token chlorpromazine proved to be better and reserpine worse than the placebo.

Similar calculations are recorded in Table III, where the response to each drug is considered relative to the rating actually obtained at the beginning of each period.

TABLE III

CLINICAL RESPONSE OF ALL PATIENTS TO ALL DRUGS ASSESSED BY RATINGS COMPARED WITH CONDITION BEFORE ADMINISTRATION OF DRUG

Drug Employed	Responses		
	Unchanged	Improved	Worse
Chlorpromazine	7	14	3
Reserpine	5	6	13
Placebo	13	8	3

The result shows a significant difference ($\chi^2 = 18{\cdot}40$, d.f. $= 4$, $P < 0{\cdot}002$) in the same direction as in Table II and so indicates that the order of administration did not exercise an influence on the responses observed.

The extreme rating categories are of some interest. Seven patients were rated as a+ at some time during the 18 weeks. If this response is attributed only to that substance given to a patient not rated as a+ before its administration, then the response was associated with six patients on chlorpromazine, one patient on reserpine, and no patient on placebo. It is unlikely that such a distribution among the substances is due to chance ($P = 0{\cdot}02$). The mean length of stay of these seven patients up to the beginning of treatment was 12·5 years compared with 17·2 years for the remainder, a difference which just fails to achieve significance ($t = 1{\cdot}81$; $0{\cdot}1 > P > 0{\cdot}05$). A rating of c− was only given to four patients who were receiving reserpine.

Discussion

The results serve to indicate that in this sample of patients chlorpromazine was the drug of choice, for its administration was associated with a higher degree of improvement and a lower degree of toxicity than that of reserpine.

No precise comparisons can be made with the results of other workers as it was possible to extract relevant statistics from only one paper, that of Campden-Main and Wegielski (1955). Table IV displays the results obtained in the treatment of schizophrenia with both drugs, taken from several papers, expressed in percentages and arranged in three degrees of improvement corresponding approximately to our own. The different methods used by the various authors render stricter comparison impossible: controlled experiment was attempted in only two studies.

TABLE IV

COMPARISON OF PUBLISHED THERAPEUTIC RESULTS OBTAINED WITH CHLORPROMAZINE AND RESERPINE IN THE TREATMENT OF SCHIZOPHRENIA

Author	Number of Patients	Drug	% Marked Improvement	% Moderate Improvement	% Slight Improvement
Hollister *et al.*	127	Reserpine	17	29	31
Kline and Stanley	126	,,	20·6	40·5	23·8
Kinross-Wright	27	,,	29	40	—
Tasher and Chermak	214	,,	36	30	—
Campden-Main *et al.*†	41*	,,	9·5	29	67
Barsa and Kline	150	,,	23	43	25
Noce *et al.*	165	,,	36	28	20
Glynn	75	,,	36	44	20
Present authors†	24	,,	13 (a+)	17 (b+)	21 (c+)
Kinross-Wright	97	Chlorpromazine	35	37	20
Vaughan *et al.*†	103	,,	27	43	—
Goldman	201	,,	19	16	47
Labhardt	106	,,	18	40	26
Present authors†	24	,,	25 (a+)	25 (b+)	13 (c+)

† Controlled study.
* One-third of these were affective disorders.

It will be seen that the figures for chlorpromazine in the present study are within 10% of others published. Kinross-Wright (1955) has also compared the efficacy of reserpine and chlorpromazine in the treatment of schizophrenics and found that chlorpromazine produced marked improvement in a larger number of cases. The results we have obtained with reserpine, on the other hand, are less satisfactory than those in most studies published hitherto. The more frequent toxic effects of the drug were responsible for this finding. During the treatment of only one case was chlorpromazine discontinued because of toxic effects, which have been fully discussed by Lomas, Boardman, and Markowe (1955). Reserpine had to be reduced on this account from 15 mg. to 10 mg. daily in three cases and from

10 mg. to 5 mg. daily in four cases. In five cases it was withdrawn.

The most important evidence of toxicity was the appearance of a Parkinsonian syndrome, which was observed in six patients receiving reserpine and in one patient receiving chlorpromazine. These patients all exhibited tremor, rigidity, bowed posture, immobile facies, loss or diminution of associated limb movements, and excessive salivation, resulting in an unmistakable and striking clinical picture. It is noteworthy that in one case the Parkinsonian syndrome made its appearance while the patient was receiving chlorpromazine and became more severe when reserpine was administered. In every case the symptoms disappeared when the drug was withdrawn. The only other undesirable effect of chlorpromazine was an oedema of the face which developed in one patient and subsided when the drug was discontinued.

The undesirable side-effects of reserpine were more numerous and more disturbing. They included restlessness (one case), incontinence of faeces (one case), and of urine (two cases), excessive salivation (three cases), bulimia (five cases), oedema of the face and epilepsy (one case). All these complications have been described by other authors (Barsa and Kline; Kinross-Wright).

From our experience it would appear, therefore, that a daily dose of 10-15 mg. reserpine by the oral route is too large. This inference is not supported by the reports of other authors. Kinross-Wright (1955), using doses up to 60 mg. daily, found no evidence of Parkinsonism until a dose of 30 mg. daily had been reached. Noce and others (1955) employed 2·5-10 mg. daily, noted minor side-effects only, and did not report Parkinsonism at all. Barsa and Kline (1955) state that of 200 patients, treated with up to 13 mg. reserpine daily, only five developed epilepsy and 10 Parkinsonism. Hollister and others (1955) obtained poor results with an oral dose of 1 to 4 mg. which they therefore increased to 5 mg. daily parenterally with an additional 2-8 mg. by mouth: the side-effects were slight and necessitated withdrawal of the drug in only one case; no Parkinsonism or epilepsy was noted in 127 cases treated. Glynn (1955) noticed no untoward side-effects using 5-15 mg. daily. Finally, in a clinical trial recently carried out at Netherne Hospital toxic effects of the reserpine were frequent but less troublesome, though Parkinsonian symptoms were prominent (personal communication).

No satisfactory explanation for these differences can be offered because of the obscurity attending the mode of action of reserpine (*Lancet*, 1955). Clinically it may be significant that the schizophrenic patients of the present study were chosen not for their aggressiveness and over-activity, as in most of the other studies cited, but on account of their apathy and inertia: such symptomatic differences may be token factors in the nature or phase of the schizophrenic illness which bear on the response to the drugs employed. Within the group reactions to the placebo also occurred in a number of cases (see Table I) and individual variation in response to both drugs was evident. The shorter mean hospital stay of those patients who achieved an a+ rating may be of some significance in this regard. Labhardt (1954) has reported a similar finding in patients whose stay in hospital was shorter. An adequate interpretation of group and individual difference must, however, await the results of further research.

Summary

A clinical trial designed to compare the efficacy of chlorpromazine and reserpine in the treatment of 24 chronic schizophrenic patients has been described.

The results indicate that chlorpromazine was responsible for improvement in a significantly higher proportion of cases than reserpine and that, in the doses employed, reserpine was responsible for the great majority of toxic effects observed.

Thanks are due to Messrs. Ciba for supplying " serpasil " and dummy tablets and to Messrs. May and Baker for supplying dummy tablets.

REFERENCES

Anton-Stephens, D. (1954). *J. ment. Sci.*, **100**, 543.
Barsa, J. A., and Kline, N. S. (1955). *J. Amer. med. Ass.*, **158**, 110.
Campden-Main, B. C., and Wegielski, Z. (1955). *Ann. N.Y. Acad. Sci.*, **61** (art. 1), p. 117.
Charatan, F. B. E. (1954). *J. ment. Sci.*, **100**, 882.
Foote, E. S. (1955). *Brit. med. J.*, **1**, 1192.
Glynn, J. D. (1955). *Journal of Neurology, Neurosurgery and Psychiatry*, **18**, 225.
Goldman, D. (1955). *J. Amer. med. Ass.*, **157**, 1274.
Hollister, L. E., Krieger, G. E., Kringel, A., and Roberts, R. H. (1955). *Ann. N.Y. Acad. Sci.*, **61** (1), 92.
Kinross-Wright, V. (1955). *Ibid.*, **61** (1), 174.
Kline, N. S. (1954). *Ibid.*, **59** (art. 1), 107.
——, and Stanley, A. M. (1955). *Ibid.*, **61** (1), 85.
Labhardt, F. (1954). *Schweiz. Arch. Neurol. Psychiat.*, **73**, 309.
Lancet (1955). **2**, 330. (Leading article).
Lomas, J., Boardman, R. H., and Markowe, M. (1955). *Lancet*, **1**, 1144.
Noce, R. H., Williams, D. B., and Rapaport, W. (1955). *J. Amer. med. Ass.*, **158**, 11.
Tasher, D. C., and Chermak, M. W. (1955). *Ann. N.Y. Acad.Sci.*, **61** (1), 108.
Vaughan, G. F., Leiberman, D. M., and Cook, L. C. (1955). *Lancet*, **1**, 1083.

BOOK REVIEWS

Les Grandes Activités du Lobe Temporal. Edited by T. Alajouanine. (Pp. 298; 94 figures. Fr. frs. 2,200.-.) Paris: Masson et Cie. 1955.

This book is a collection of essays on the structure and functions of the temporal lobe. The recent interest aroused in the temporal lobe epilepsies and their possible surgical treatment has evidently prompted the work. The gross anatomy of the lobe and its connexions are considered, and recent work on the rhinencephalon and hippocampal formation are reviewed. The importance of its connexions with other cortical areas, and the fact that it develops in size and complexity as the mammalian scale is ascended, are emphasized. The evidence from physiological neuronography is mentioned which suggests that the lobe has important connexions both with brain-stem centres and with the orbital aspects of the frontal lobe. Professor Gastaut reviews his extensive work on paroxysmal discharges in the temporal cortex and the evidence that these can arise from deeper structures both in the amygdaloid and hippocampal nuclei and also in thalamic and mesencephalic regions, while Moruzzi considers its association with the reticular formation and also takes the opportunity of giving a more general review of the latter's function. The part played by the temporal lobe in autonomic integration and in the somatic changes associated with emotion are discussed by Professor Monnier. The functions of this region as an auditory reception area and its part in speech and its disturbance in aphasia are fully considered. Recent developments in intracellular recording of both spontaneous and evoked response are briefly discussed. An essay by Grey Walter on the analysis of cortical electrical activity by means of the " toposcope ", and one on the central coordination of posture and movement by McCulloch are also included.

The book will be of value to neurologists, since it assembles much otherwise scattered work. They will, however, have to apply at times a critical faculty which some contributors do not evince.

Formen des Posttraumatischen Kopfschmerzes. By Elmar Bues. (Pp. xii + 111; 28 figures. DM 9.60.) Stuttgart: Georg Thieme Verlag. 1956.

This is a somewhat unimaginative account of various types of post-traumatic headache, and the forms of treatment considered are mainly concerned with cutting something, with special reference to branches of the trigeminal nerve.

Diseases of the Nervous System, 5th ed. By Sir Russell Brain. (Pp. xviii + 996; 90 figures. 55*s*.) London: Oxford University Press. 1955.

It is over 20 years since this well-known textbook first appeared, and the latest edition maintains the high standard expected. It is no easy matter to keep a textbook up to date, and it is perhaps inevitable that some sections appear to be disappointing. Thus the section on headache (p. 286) gives an inadequate account of the modern methods of investigating and treating head pains. The section on myelitis pays little attention to vascular aetiology; occupational cramps are dismissed as a neurosis; cough syncope is not considered; the section on shoulder girdle neuritis is vague, and in considering epilepsy auras are given little attention.

There is an inaccuracy on p. 179 regarding Bell's palsy, where it is stated that if reaction of degeneration is complete at three weeks " recovery is unlikely ": in fact, these cases mostly recover quite well by regeneration.

However, it is easy to find something to criticize in a textbook. An enormous amount of information is presented, and this work is still the standard British work on neurology.

Die Zerebralen Herdstörungen bei Hinterhauptsverletzungen und ihre Beurteilung. By Clemens Faust. (Pp. viii + 111; 41 figures. DM 14.70.) Stuttgart: Georg Thieme Verlag. 1955.

This small work reports a clinical study of a series of cases of brain wound of the occipital region. The higher mechanisms such as object agnosia and alexia are specially considered, and the methods used include tachistoscopic examination. The perimetric studies and anatomical details are unfortunately inadequate for full appreciation of the clinical material.

Klinische Psychopathologie. By Kurt Schneider. (Pp. 188. DM 12.80.) Stuttgart: Georg Thieme Verlag. 1955.

Although many sections of this book have been published independently, it now provides a useful synthesis of Professor Schneider's current views on clinical psychopathology. They do not differ in essentials from those he put forward 30 years ago, but they have matured in the soil of his clinical experience. Though simply expressed, they embody much reflection and a consistent, well-developed theory which is, however, too abstract to be acceptable to English psychiatrists. In view of Professor Schneider's unrivalled contributions to the description and clarification of psychopathic personalities, it is of considerable interest to find him here deprecating the use of the term in forensic and other reports because it has come more and more to connote an adverse ethical or social judgment: like " hysteria " it has lost its proper medical significance and incorporated moral values which make it a dangerous word for doctors to use. Types of

psychopathy are in his view very different from diagnoses of disease. He regards all diseases as having a somatic basis, and so he distinguishes sharply between abnormal and morbid; personality can be abnormal without being morbid. The forensic implications of his opinion are far-reaching. On many other crucial issues in psychiatry his views, though opposed to those current among us, bring the problems into sharper focus and offer an intelligent, clinically expert, and coherent alternative.

Lehrbuch der Allgemeinen Psychopathologie. Grundbegriffe und Klinik. By K. W. Bash; Foreword by Prof. H. Binder. (Pp. xvi + 288; 10 figures. DM. 29.50.) Stuttgart: Georg Thieme Verlag. 1955.

The width of the gap separating psychopathology in the English-speaking countries from the same subject in German-speaking countries is plainly shown by this thoughtful and ambitious work. The author, a Swiss psychiatrist and a pupil of C. G. Jung, has sought to bring psychology and psychiatry together, making use of "depth-psychology" and *Gestalt* psychology for the purpose. The aim is not dissimilar from that of certain British and American writers, but the execution is very different. The extensive output of psychological research into the abnormal as well as the normal during the last 15 years is given very scanty recognition, and national or linguistic boundaries seem to be an obstruction to the writer's outlook: thus such notable contributors to psychopathology as Eugene Minkowski, Clérambault, and Henri Ey are not mentioned. In spite of these limitations, the book deserves the attention of English readers because it does not run along well-worn tracks, it is scholarly, and provides an orderly, clinically relevant statement of the theoretical position held by an important group of Swiss-German psychopathologists.

The Interpersonal Theory of Psychiatry. By Harry Stack Sullivan. Edited by Helen Swick Perry and Mary Ladd Gawel, with an Introduction by Mabel Blake Cohen. (Pp. xviii + 393. 35*s*.) London : Tavistock Publications. 1955.

Conceptions of Modern Psychiatry, 2nd ed. By Harry Stack Sullivan; with a Foreword by the Author and a critical appraisal of the Theory by Patrick Mullahy. (Pp. xiii + 298. 32*s*. 6*d*.) London: Tavistock Publications. 1955.

Dr. Sullivan powerfully furthered the growth in the United States of a form of "dynamic" psychiatry and psychology which tried to integrate psychoanalysis with the social sciences. Like Karen Horney and Eric Fromm, Sullivan stressed the cultural forces which influence relations between people and promote the successive stages of mental development. He was averse from speculative excursions, but formulated, on the basis of his clinical experience, a systematic theory of interpersonal relations. Personality, he taught, derives from the continuous impact of personal and social forces upon the growing individual, who is mainly concerned with the pursuit of satisfactions and of security. Psychological troubles arise because the aim of security is not attained, or because there is conflict between the search for satisfactions and pressure to conform to the cultural pattern of the milieu. Elaborately worked out in the two sets of lectures which these books contain, Sullivan's views offer a stimulating and intelligible alternative to the abstruse complexity of orthodox psychoanalysis.

Psychomotor Aspects of Mental Disease. An Experimental Study. By H. E. King. (Pp. xiv + 185. 28*s*.; $3.50.) Cambridge, Mass.: Harvard University Press; London: Oxford University Press. 1955.

This excellent inquiry shows once more how experimental psychology is coming into its own again in psychiatric research after the long period of neglect which followed the researches of Kraepelin, Rivers, and others whom Wundt had directly or indirectly influenced.

Dr. King decided to study the fine movement patterns in which strength is secondary to speed or precision. Three factors were investigated, concerned respectively with speed of single reaction, speed of stereotyped oscillatory movement (tapping), and precision (manual dexterity). These factors were examined in normal, chronic schizophrenic, and neurotic subjects by means of a battery of suitable tests. The schizophrenics were retarded in their performance on all tests when compared with the normals, and their degree of retardation corresponded to the clinical severity of their disturbed behaviour. In a lucid and erudite discussion of the findings Dr. King concludes that the faulty psychomotor performance of the patients indicates a disturbance in the basic process of adaptation effected through motor adjustment to the environment. The monograph is, within its stated limits, a model of systematic experimental inquiry into a facet of mental disorder.

Grundfragen der Neurosenlehre. By J. H. Schultz. (Pp. xii + 215. DM 24.-.) Stuttgart: Georg Thieme Verlag. 1955.

Since the publication of his textbook of psychotherapy in 1918 Dr. Schultz has been the most authoritative German spokesman of this aspect of psychiatry. In spite of comparative isolation he has maintained a lively interest in developments in other countries, and has adapted his conceptions of neurosis to bring them closer to those now prevailing elsewhere. His reading has been wide, as this introduction to medical psychology shows. It has, in common with most other books on the subject, a very large allowance of words to go with a pittance of assured fact and principle, but the seasoned reader expects that. Professor Schultz's general standpoint is close to that of Kretschmer, but with a stronger infusion of psychoanalysis.

Psychiatry for the Family Physician. By C. Knight Aldrich. (Pp. ix + 274. 43*s*.) London: McGraw-Hill Publishing Co. 1955.

This book approaches psychiatry from the psychodynamic viewpoint, but avoids the grosser extravagances of psychoanalytical doctrine. Much of the space is taken up with emotional development and there are

good chapters on the psychiatric problems of the crucial epochs in an individual's life, and the various tensions which can develop within the family group. The psychoses are dealt with more briefly.

A Manual of Psychiatry, 3rd ed. By K. R. Stallworthy. (Pp. 324. 30*s*.) New Zealand: N. M. Peryer. 1955.

This is a short textbook of psychiatry which clearly and concisely covers most of the fundamental facts of psychiatry and those branches of psychology which are relevant to the subject. The psychology is perhaps a little old-fashioned; for example, the author speaks of " instincts " where most psychologists would use the term " drives ". A more serious criticism is the inadequate treatment of the neuroses. As is inevitable in a short textbook, it is dogmatic, but this is an advantage for the people for whom it is primarily intended—nursing and medical students.

Psychological Medicine. A Short Introduction to Psychiatry, 4th ed. By Desmond Curran and Maurice Partridge. (Pp. viii + 407; 20 figures. 21*s*.) Edinburgh and London: E. & S. Livingstone. 1955.

This textbook, previously the work of Dr. Curran and the late Eric Guttmann, has been extensively rewritten and enlarged. Whereas the first edition, 18 years ago, contained 188 pages, there are here 407. The section on psychiatry in wartime has been dropped, and fuller details of physical methods of treatment included. The general features which characterized the book are unchanged: the exposition is on traditional clinical lines, psychopathology and psychotherapy receive rather cavalier treatment, recent work by psychologists and other such investigators is hardly referred to, the style is clear and straightforward with occasional lapses into the sprightly and the frivolous, and the descriptions of syndromes are good. And in all, the book remains an excellent primer of unpretentious, " down-to-earth " psychiatry.

Child Psychology, 4th ed. By Arthur T. Jersild. (Pp. xii + 676. 42*s*.) London: Staples Press. 1955.

The merit of this book lies in its breadth and tolerance. Many texts on child psychology concern themselves with development as seen from the instinctual or psychoanalytic point of view, others with the measurement of abilities and the description of behaviour: few give a fair and comprehensive review of the whole rather uncoordinated field of knowledge and speculation. Dr. Jersild covers the extensive literature with discriminating care, though a more critical exposition of the material in the three chapters on emotional development would have been to the book's advantage. The book is evidently intended mainly for teachers and others interested in educational psychology: this may account for the inadequacies of the last chapter, " Personality Problems and the Search for Self ", which is poorly documented and superficial, if read from the clinical standpoint. Conversely many child psychiatrists could profit by reading the three chapters on social relationships and social behaviour.

The Interpretation of Dreams. By Sigmund Freud. Translated and edited by James Strachey, (Pp. xxxii + 692. 21*s*.) London: Allen & Unwin. 1955.

This is a new translation of one of Freud's major works. It is a very comprehensive edition containing the changes and additions made by Freud in later years. There is an excellent introduction together with extensive bibliography and indexes.

So far as the translation itself is concerned, hardly any sentence is the same as in Brill's edition. The changes make this book longer but more readable.

The translating and editing of this work has evidently been a labour of love for Mr. Strachey and this is reflected in its excellence and comprehensiveness.

Grossen Nervenärzte. Edited by Kurt Kolle. (Pp. viii + 284; 21 illustrations. DM 29.40.) Stuttgart: Georg Thieme Verlag. 1956.

This book gives short biographies of 21 " great neurologists ", 10 of whom are Germans. The term " *Nervenärzte* " embraces psychiatrists, and Freud, Jung, Bleuler, Kraepelin, and Jaspers are included. Sherrington, Pawlow, and Cajal are also represented. Each essay is illustrated with a portrait and the book is well produced. Some of the essays are by acknowledged authorities on their subject—Gordon Holmes on Hughlings Jackson, for instance.

James Parkinson 1755-1824. Edited by Macdonald Critchley. (Pp. xvi + 268. 15*s*.) London: Macmillan & Co. 1955.

This little book consists mainly of a reprint of the original " Essay on the Shaking Palsy " by Dr. James Parkinson, and a short biographical essay on the author by Dr. W. H. McMenemey. In addition there are notes on the clinical features of " Parkinsonism " by Sir Francis Walshe and on the pathology of the condition by Dr. J. G. Greenfield.

Parkinson seems to have been a man of many interests which included an active part in the radical politics of his day (1755-1824). His essay illustrates both the advantages and the pitfalls of the purely clinical observational method for, as he says himself, anatomical (post-mortem) studies were not available.

J-M. Charcot (1825-1893)—Sa Vie—Son Oeuvre. By Georges Guillain. (Pp. 188; 9 figures. Fr. frs. 1,400.-.) Paris: Masson et Cie. 1955.

This book gives a biographical note on Charcot and brief synopses or reviews of his major medical works. The biographical details are scrappy, and although they are filled out by quotations from his pupils they do not give any clear impression of Charcot's personality. A quarrel with one of his former pupils, Charles Bouchard, is mentioned as being exceptional for Charcot, but even here the grounds for the quarrel seem to be unknown. It is fairly certain that much criticism must have been aroused among his colleagues over the Salpêtrière demonstrations in hypnotism—especially as stage hypnotists of the time would advertise performances

"après les expériences de Charcot" ; but nothing of this emerges in this colourless essay. A vivid description of his death during an attack of cardiac asthma is given.

After some 70 pages of biography 110 are given to a review of his writings. These contain interesting brief résumés of his work, but there is no attempt at critical appreciation.

I. P. Pavlov: Selected Works. (Pp. 654. 10*s.* 6*d.*) London: Central Books. 1956.

This is said to be the most representative selection of Pavlov's work yet published in English, and as such will be welcomed by students of brain mechanisms. Pavlov systematically waged war against those who insisted on separating mind from brain, and psychology from physiology. This brought Pavlov into conflict with some views expressed by Sherrington, and also with many conceptions expounded by psychiatrists, and his comments are vividly reported in the chapters of this book. Unfortunately there is no index to assist reference.

Suicide in London. An Ecological Study by Peter Sainsbury. Maudsley Monographs No. 1. (Pp. 116. 15*s.*) London: Chapman & Hall. 1955.

The Institute of Psychiatry now plays a leading part in the furtherance of many of the research problems related to psychiatry and neurophysiology, and the launching of a monograph series is a happy indication of the strength of the Institute and the amount of research being done. This Maudsley Monograph No. 1 is excellently presented and published, yet the cost is low when related to other comparable series.

With regard to the monograph itself, suicide being unequivocal and notifiable, it is a most suitable basis on which to study the relationship between human behaviour and different forms of neighbourhood in London. The effect of social isolation, social mobility, poverty, misfortune, social class, unemployment, divorce, illegitimacy, and mental illness are all presented statistically, and thus provide an invaluable insight into many modern social problems.

Management of Addictions. Edited by Edward Podolsky. (Pp. xvii + 413. $7.50.) New York: Philosophical Library. 1955.

These articles, collected from 19 journals and reprinted without change, lack cohesion and orderly sequence; the level at which the writers present their evidence and conclusions varies widely; there is no subject index; and there is much repetition of commonplaces. Although a few of the authors are distinguished, the compilation is too uneven and unplanned to be useful either to the expert in this field or to the uninformed reader.

Biochemistry and the Central Nervous System. By Henry McIlwain. (Pp. vii + 272; 43 figures. 40*s.*) London: J. & A. Churchill. 1955.

There have recently been many points of biochemical research which have direct contact with clinical conditions of the nervous system. The copper and amino-acid metabolism upsets of Kinnier Wilson's disease, the enzyme and co-enzyme system abnormalities in certain forms of neuropathy, and the abnormality of cholinesterase content in excised cerebral scars are some examples, and there are many more.

A book dealing specifically with the biochemistry of the nervous system is therefore timely, and this is one of several produced recently. It covers the ground adequately from the clinician's point of view, and its range of references makes it useful also as an introduction to a rather wider field of biochemistry in medicine.

Thallium Poisoning. By J. J. G. Prick, W. G. Sillevis Smitt, and L. Muller. (Pp. vi + 155; 21 figures. 19*s.*) Amsterdam: Elsevier Publishing Company; London: Cleaver-Hume Press. 1955.

This small book reports the clinical features of thallium poisoning, and emphasizes its sinister possibilities. Polyneuritis is the commonest neurological effect and may cause death by respiratory failure. Thallium compounds are all too easily obtainable and are used in rat poisons.

Electrochemistry in Biology and Medicine. Edited by Theodore Shedlovsky. (Pp. xii + 369; illustrated. 84*s.*) London: Chapman & Hall; New York: John Wiley. 1955.

This book is based on the Symposium on Electrochemistry in Biology and Medicine held in New York in 1953. There are 19 separate contributions which present modern thought on electrochemical problems of living processes.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Die Schadelhirntrauma. By Erich Hatzenstein. (Pp. 992; 592 figures.) Basel: Benno Schwabe.

On the Early Development of Mind. By Edward Glover. (Pp. 483; 6 figures. 45*s.*) London: Imago Publishing Co. 1956.

The Blood-Brain Barrier. By Louis Bakay. (Pp. xii + 154; 32 figures. 40*s.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1956.

The Relationship Between Syringomyelia and Neoplasm. By Charles M. Poser. (Pp. ix + 98; illustrated. 25*s.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1956.

Clinical Studies in Neurology. By Harry Lee Parker. (Pp. xiii + 364. 47*s.* 6*d.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas.

Mental Health. (2*s.*) Published by *The Twentieth Century*, London. May, 1956.

Introduction to Psychopathology, 2nd ed. By Lawrence I. O'Kelly and Frederick A. Muckler. (Pp. xi + 704. 50*s*.) London: Staples Press. 1956.

Masked Epilepsy. By Hugh R. E. Wallis. (Pp. x + 51. 7*s*.) Edinburgh and London: E. & S. Livingstone. 1956.

Psychology of Exceptional Children and Youth. Edited by William Cruickshank. (Pp. xiii + 594; 24 figures. 50*s*.) London: Staples Press. 1956.

Progress in Clinical Psychology, Vol. II. Edited by Daniel Brower and Lawrence E. Abt. (Pp. viii + 364. $7.75.) New York: Grune & Stratton. 1956.

A Primer of Freudian Psychology. By Calvin S. Hall. (Pp. xii + 137. 13*s*. 6*d*.) London: Allen & Unwin. 1956.

Medical Research: A Mid-Century Survey. The American Foundation, Vols. I and II. (Pp. 765 and 740 respectively. 105*s*.) London: J. & A. Churchill; Boston and Toronto: Little, Brown & Co. 1956.

The Sequelae of Amputation. By Keith C. Bradley. (Pp. 236. Aust. £-. 10*s*.) Published by the Trustees of the Services Canteens Trust Fund, Australia House, London.

Hypothalamic-Hypophysical Interrelationships. Compiled and edited by William S. Fields, Roger Guillemin, and Charles A. Carton. (Pp. ix + 156; illustrated. 36*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1956.

Les Mécanismes Cérébraux de la Prise de Conscience. By Paul Chauchard. (Pp. 240. Fr.fr. 1,300.-*s*.) Paris: Masson et Cie. 1956.

Physics, Psychology and Medicine. By J. H. Woodger. (Pp. x + 146. 8*s*. 6*d*.) London: Cambridge University Press. 1956.

Regeneration in the Central Nervous System. Edited by William F. Windle; with a Foreword by Pearce Bailey. (Pp. vi + 311; 68 figures. 69*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1955.

Psychopathology of Children with Organic Brain Disorders. By Lauretta Bender. (Pp. xi + 151; 23 figures. 40*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1956.

THE MAY (1956) ISSUE

The May (1956) issue contains the following papers:—

Observations on the Extended Use of the Marchi Method. Marion C. Smith.

The Recognition and Prevention of Artefacts of the Marchi Method. Marion C. Smith.

Studies in Sensation: Observations on the Localization of the Sensations of Touch and Prick. John Marshall.

Reference of Sensation at the Spinal Level. P. W. Nathan.

Awareness of Bladder Filling with Divided Sensory Tract. P. W. Nathan.

Two Cases of Myopathy Limited to the Quadriceps. John N. Walton.

A Study of 25 Cases of Compression of the Cauda Equina by Prolapsed Intervertebral Discs. W. Bryan Jennett.

E.E.G. Abnormalities from the Temporal Lobe Studied with Sphenoidal Electrodes. G. Pampiglione and J. Kerridge.

The Effect of Insulin Coma and E.C.T. on the Short-term Prognosis of Schizophrenia. J. Hoenig, D. M. Leiberman, and I. Auerbach.

Sodium Amytal and Behaviour in Neurotic Subjects. S. G. Laverty and C. M. Franks.

Disseminated Sclerosis Treated with Isoniazid with a Method of Evaluating Chronic Neurological Disorders. Barbara M. Ansell and Edwin Clarke.

Ischaemic and Post-ischaemic Parasthesiae: Normal Responses in the Upper Limb with Special Reference to the Effect of Age. E. W. Poole.

Familial Peroneal Muscular Atrophy and Its Association with the Familial Ataxias and Tremor and Longevity. Raymond Hierons.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12*s*. 6*d*.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 241

PEARLY TUMOURS IN RELATION TO THE CENTRAL NERVOUS SYSTEM

BY

JOHN S. TYTUS and JOE PENNYBACKER

From the Department of Neurological Surgery, Radcliffe Infirmary, Oxford

In 1829 Cruveilhier described a growth found at the base of the brain, displacing the third ventricle superiorly and extending as far anteriorly as the sella turcica (Fig. 1). Its external surface was of a "metallic sheen like silver—or like a pearl of the finest water". The contents of the growth were analysed by Bannel and "presented all the characters of cholesterin". Cruveilhier also discussed a similar lesion reported a year before by La Prestre and one supposedly from Dupuytren's clinic exhibited as a wax model by Dumeril in 1807. Because of their striking external appearance he called them pearly tumours.

Verattus in 1745 is said to be the first to record such a lesion when he found at necropsy a brain tumour containing masses of hair.

Müller (1838) reported two examples and, because of the nature of their contents, named them cholesteatomas.

Virchow (1855) discussed a number of these cases, but because he failed to demonstrate cholesterin in all of them believed the term "pearly tumour" to be more suitable.

The origin of these tumours remained obscure until 1854, when von Remak suggested that they might arise from misplaced epithelial tissue. This work was substantiated by Bostroem, who in 1897 agreed with their epithelial origin. He thought that growths, which he termed "pial epidermoids", arose from embryonic skin elements at a comparatively late stage, whereas the pial dermoids arose from cell rests included earlier in embryonic life.

In 1920 Bailey, in a full discussion of these tumours, mentioned two examples, similar to Bostroem's pial epidermoids, operated upon by Cushing, but because of the existing confusion concerning their origin he retained the name "pearly tumour".

We also prefer this term and include under this heading growths of both epidermal and dermal origin, that is to say, epidermoids and dermoids.

Origin

It is now generally accepted that these tumours arise from epithelial rests that result from defective closure of the neural tube between the third and fifth week of embryonic life. Foetal implantations early in this period tend to lie in the midline, especially in the creases between the primary cerebral vesicles. If they occur later, during the formation of the secondary cerebral vesicles, they tend to lie laterally away from the midline (Bostroem, 1897). Should implantation occur after the cerebral cortex and cerebellum have formed, the rests may be deposited in mesodermal structures between skin and brain and give rise to the epidural, intradiploic, and pericranial tumours (Harvey and Burr, 1926; Rand and Reeves, 1943).

If the cleavage of cutaneous and neural ectoderm remains incomplete at a certain point a dermal sinus will develop connecting the external skin with the neuraxis (List, 1941; Walker and Bucy, 1934).

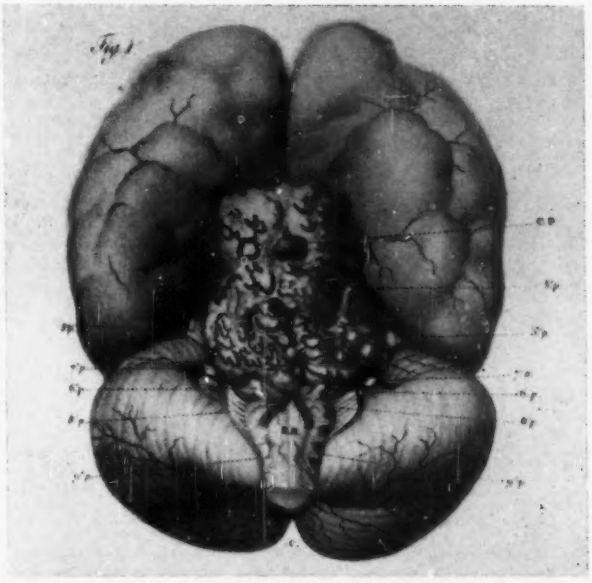


FIG. 1.—Reproduction of an illustration of Cruveilhier's case of a pearly tumour arising at the base of the brain.
[From Cruveilhier, *Anatomie Pathologique du Corps Humain*, Vol. I, Book 2, Plate 6.]

Appearance

Grossly, the epidermoids and dermoids are quite similar. Their most characteristic feature lies in the appearance of the capsule, which typically is opaque, white, and glistening. Variations in colour do occur, however, especially in the dermoids. They may be grey, yellow, green, brown, or even red (King, 1939).

The main tumour mass is made up of epithelial debris which slowly accumulates within the capsule from desquamating cells of the epithelial lining. It contains fatty material and cholesterol, and in the case of the dermoids sebaceous material and hair. The consistency depends upon the proportions of these substances (Brock and Klenke, 1931). It is usually caseous or like soft butter, but, especially in the dermoids, may be cystic, containing oily or opalescent yellow fluid.

The capsule is a thin membrane which, in the case of epidermoids, consists of an epidermal layer without dermal structures (Fig. 11). Dermoids, on the other hand, have a capsule composed of epidermis, together with a dermal layer containing hair and sebaceous glands (Fig. 19). Fat and connective tissue may also be present.

Both types seem similar to the naked eye, and since their characteristics are the same as regards growth, recurrence, and complications, it seems unnecessary to make a sharp distinction between the two (Bailey, 1924; Bostroem, 1897; Critchley and Ferguson, 1928; Horrax, 1922; Montgomery and Finlayson, 1934).

Characteristics

They are benign encapsulated tumours that usually do not invade surrounding regions. Raskin (1949), however, described a case in which an epidermoid had directly infiltrated the brain, and cites other examples. Rarely, they undergo malignant change (Ernst, 1912; Hug, 1942; Stromeyer, 1909). They are extremely slow-growing and, depending on their location, may attain a tremendous size before any signs of their presence appear. Occasionally, they become calcified (Peyton and Baker, 1942; Rand and Reeves, 1943).

Their incidence ranges between 0·3 and 1·8% in various reported series of tumours of the central nervous system (Findeisen and Tönnis, 1937; King, 1939; Mahoney, 1936; Sachs and Horrax, 1949; Walker and Bucy, 1934).

Clinical Data

This series comprises a total of 41 cases of verified epidermoids and dermoids, most of which were seen at the Radcliffe Infirmary. Four patients, however, were treated at the London Hospital, and two were operated upon at St. Hugh's Military Hospital during the war.

Although theoretically they may occur at almost any site in the central nervous system, certain locations are more common. They most frequently occur in the subarachnoid cisterns at the base of the brain, but are not infrequently found in the pericranial, orbital, petrous, and diploic regions and in the cerebello-pontine angle. They are also seen in the substance of the cerebral cortex, cerebellum, and in the spinal canal.

Pericranial.—These growths were found in two children (R.I. Nos. 53428/46 and 177532) 3 and 5 years of age. Each presented with a mass near the midline over the vertex of the skull in the region of the anterior fontanelle (Fig. 2). This had been

FIG. 2

FIG. 2.—Photograph of a child (R.I. 53428/46) with a pericranial dermoid. Note its midline position and its relation to the anterior fontanelle.

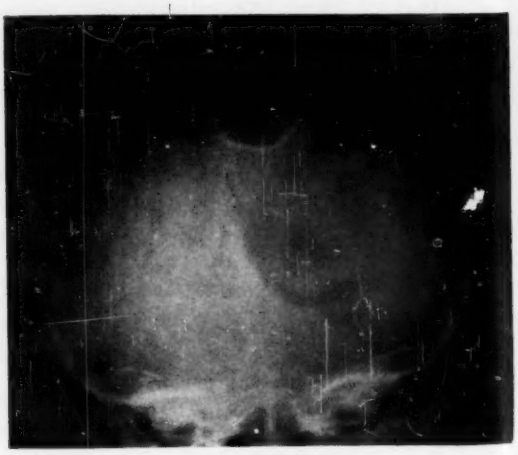


FIG. 3

FIG. 3.—Skull radiograph (same case) showing bony defect in a pericranial dermoid. Note smooth edges that appear to be eroded from without inwards. The tumour itself can also be seen.

FIG. 4.—Drawing to show the usual location of an orbital dermoid and its relation to the glove and periorbital structures.
[From Cairns, H. "Peripheral Ocular Palsies from the Neurosurgical Point of View," *Trans. ophthal. Soc. U.K.*, 1938, 58, 464-482 (Fig. 172). By permission of the Editor.]

FIG. 5.—Skull radiograph showing the characteristic appearance of an orbital pearly tumour (Case 2). There is a circumscribed erosion of the left supra-orbital ridge and the margins of the defect are smooth and thickened.

present since birth in each case and had gradually increased in size. There were no neurological abnormalities.

Skull radiographs revealed a round bony defect that appeared to erode both the inner and outer tables (Fig. 3). In both cases the cortex of the bone appeared to be eroded from without in. This particular characteristic aids in the differentiation of these lesions from encephaloceles and also raises a point in aetiology. The apparent origin of these tumours from the pericranium substantiates the work of Harvey and Burr (1926), who proved that the neural crest contributes ectodermal elements to the mesoderm that take part in the formation of the meninges. Epithelial implantations in relation to the dura or the pericranium therefore become understandable.

The tumours were removed easily and without event. Their gross appearance was characteristic. Histological examination of both specimens revealed them to be dermoids.

Orbital.—These tumours usually arise from the lateral orbital roof (Fig. 4).

They tend to grow very slowly, displacing the eye downwards and slightly medially, and are characterized by unilateral proptosis of long duration without neurological symptoms. Visual acuity is often unaffected and, because of their slow growth, these lesions rarely cause double vision.

Six patients in this series had orbital pearly tumours (Table I). Proptosis was the main complaint in all cases. In five it was painless. One patient (Case 3) also complained of headaches, but the neoplasm had extended posteriorly to involve the sphenoidal ridge. The length of the history varied from 15 months to 20 years, the average duration of symptoms being about four years.

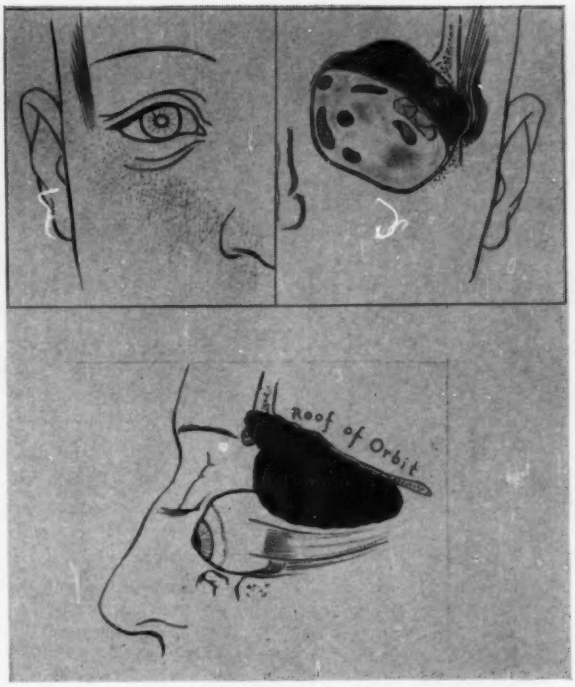


FIG. 4

FIG. 5

TABLE I
ORBITAL PEARLY TUMOURS

	Age	Sex	Duration of Symptoms (yr.)	Visual Loss	Diplopia	C.S.F. Protein (mg./100 ml.)	Estimated Removal	Type	Years Followed
1. J.H., L.H.	57	M	7	No	Yes (mild)	45	Complete	Dermoid	10
2. E.B. (R.I. No. 3966/43)	38	F	20	No	Yes (mild)	43	Complete	Epidermoid	13
3. G.G. (R.I. No. 48074/45)	28	F	2	No	No	—	Complete	Epidermoid	11
4. A.M. (R.I. No. 100641/49)	36	F	6	Yes	No	—	Complete	Dermoid	—
5. R.C. (R.I. No. 127413)	29	M	7	Yes	No	30	Complete	No capsule found	6
6. F.P. (R.I. No. 213947)	24	M	1½	No	No	25	Complete	Dermoid	½

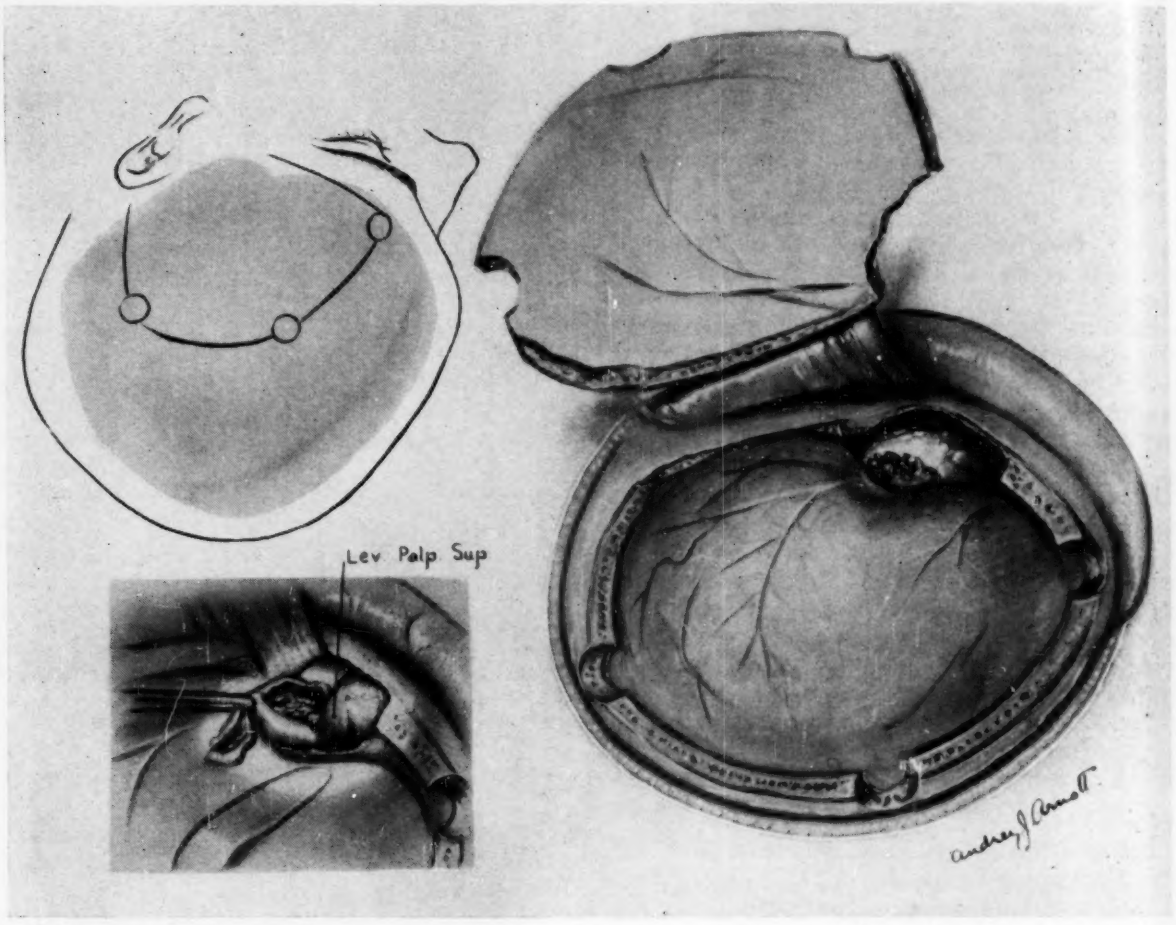


FIG. 6.—Drawing of the operative approach to an orbital pearly tumour. A frontal flap is turned and the orbit is unroofed. By exposing the anterior fossa intracranial extensions of these tumours can also be dealt with.

Visual acuity was normal in four patients. In two cases there was moderate visual loss, without demonstrable scotoma or other evidence of optic nerve involvement. In one, vision had returned to normal at the time of discharge, and it was presumed that the previous visual loss had been a factor of the proptosis. None of these patients complained of double vision, but in two of them it could be elicited by upward movement of the eyes.

As one would expect, the cerebrospinal fluid protein level, obtained in four patients, was not elevated in any of them.

Orbital radiographs usually reveal a circumscribed area of erosion of the supraorbital ridge (Fig. 5). The margins of the defect tend to be rounded, smooth, and thickened, evidence of long-standing involvement. There may be scalloping of the edges, and trabeculation is occasionally seen.

The unsightly proptosis constitutes the chief indication for surgical removal of these tumours. They can best be dealt with through a frontal craniotomy approaching the orbit from above (Fig. 6). This affords access to the anterior fossa in the event that an intracranial extension is found.

Total removal is usually possible and was believed to have been achieved in all of these cases. There have been no known recurrences to date. From the cosmetic standpoint gratifying results may be obtained (Figs. 7 and 8).

Histologically, three of the tumours were dermoids, two were epidermoids, and in the sixth patient no capsule was available.

Petrous.—Only brief mention will be made of the petrous tumours, since three examples have already been reported by one of us (Pennybacker, 1944).

The patients usually present themselves with a progressive peripheral facial nerve paralysis, usually associated with deafness and absent caloric responses on the same side. There are seldom other neurological abnormalities, and the cerebrospinal fluid

FIG. 7.—Pre- and post-operative photographs of a patient with an orbital dermoid (Case 4).

FIG. 8.—Pre- and post-operative photographs of a patient with an orbital dermoid (Case 5). There was some visual loss but in spite of the marked displacement of the left eye he did not complain of diplopia. The last photograph was taken six years post-operatively.

FIG. 7

FIG. 8

protein is usually normal. There is frequently a past history of ear infection.

These patients are usually thought to be suffering from Bell's palsy, although the gradual onset and progression of the paralysis clearly indicate a different aetiology. Moreover, skull radiographs reveal erosion of the petrous bone that is quite characteristic (Fig. 9).

Cerebello-pontine angle tumours can be ruled out by the absence of cerebellar signs and fifth nerve involvement and by the normal cerebrospinal fluid protein.

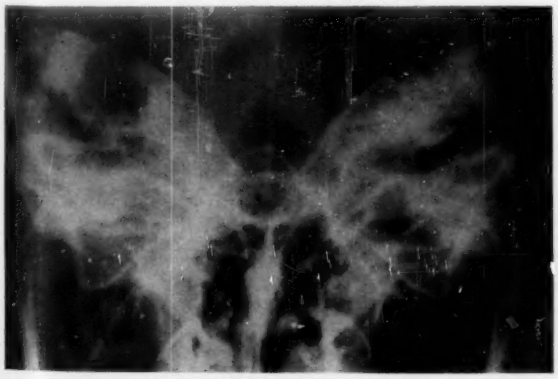


FIG. 9.—Skull radiograph of a patient with a pearly tumour involving the right petrous bone (Case 6). Pre-operatively he still retained a vestige of facial nerve function. After operation, however, there was complete paralysis, although the nerve remained in continuity. Exposure was gained through the endaural mastoid approach.

We have encountered six cases (Table II). Four of them had a past history of ear infection. In addition, one man (Case 1) had an episode of acute otitis media after the onset of facial weakness. The ear drums in all five of these patients were scarred, and in two of them perforations were present. There had never been any history of ear infection in the other patient (Case 5), and indeed he was not deaf. Total deafness, associated with absent caloric responses, was found in five patients. In the other, there was no deafness by gross testing. All of them had facial nerve paralysis, and in only one was it incomplete. The cerebrospinal fluid protein, available in five cases, was normal in all of them.

The location of these tumours is such that they can often be totally removed. This can best be accomplished through the temporal route or the combined temporal and mastoid approach, depending on their location in the petrous bone as determined by radiographs.

The main indication for operation is preservation of facial nerve function, and the chances of recovery are remote if the nerve is completely paralysed.

TABLE II
PETROUS PEARLY TUMOURS

	Age	Sex	Past Ear Infection	Deafness	Facial Nerve Paralysis	Post-operative Recovery	C.S.F. Protein (mg./100 ml.)
1. J.H. (R.I. No. 15391)	42	M	During P.I.	Yes	Complete	No	35
2. R.T. (R.I. No. 23085)	60	M	Yes	Yes	,,	Partial	30
3. G.C. (R.I. No. 5596/43)	53	M	Yes	Yes	,,	No	50
4. R.A. (R.I. No. 120535/50)	40	M	Yes	Yes	,,	No operation	58
5. G.S. (R.I. No. O.P.D.)	54	M	No	No	,,	No operation	—
6. A.H. (R.I. No. 210435)	37	M	Yes	Yes	Incomplete	Complete paralysis	65

Better results could be expected by earlier operation when only a partial paralysis exists. Four of these patients had operations for this condition, but improved facial nerve function was observed in only one case.

The origin of these tumours remains unsettled. Their relation to infection cannot be doubted, but the question arises as to cause and effect. Are they the result of middle ear or mastoid disease, or do they occur as inclusion epidermoids contributing to the otitic infection ? Some writers lean towards the latter view and make a sharp distinction between these " true epidermoids " and the middle ear " cholesteatomas " that are known to be the result of infection (Bailey, 1924; Critchley and Ferguson, 1928; Jefferson and Smalley, 1938). It has been postulated that their origin is related to the development of the middle ear (Körner, 1900, cited by Rosenwasser, 1935).

Other authors are convinced that they arise as the result of infection because of their frequent association with chronic ear disease (Grant and Austin, 1950; Love and Kernohan, 1936; Rand and Reeves, 1943).

Simpson (1954) proposed that they begin as a serous effusion into which cholesterin crystals are deposited because of a high serum cholesterol level. This in turn would evoke a foreign body reaction, and later, because of this tissue response, a metaplasia of the lining cells to epidermoid elements would occur.

Diploic.—There were no examples of diploic pearly tumours in this series, but we were fortunate enough to encounter two cases on the Neurosurgical Service at the University Hospital, Ann Arbor, Michigan. Dr. Edgar Kahn has kindly permitted us to discuss them.

One was a 67-year-old woman who presented with a soft fluctuant mass in the right parieto-occipital region of the scalp that she had noted for seven years. There were no symptoms other than the presence of the lesion itself, and neurological examination failed to reveal any abnormalities.

Skull radiographs revealed a large bony defect in the right parieto-occipital region (Fig. 10). Its margins were scalloped and thickened, and there was some suggestion of trabeculation, signs sufficiently characteristic to suggest the diagnosis preoperatively.

At operation a typical pearly tumour was found which had eroded through both the inner and outer tables of the skull. It was removed, and the bony defect repaired with acrylium. The underlying dura was found to be intact and was not opened. Her convalescence was satisfactory.

The other example was in a 60-year-old man who

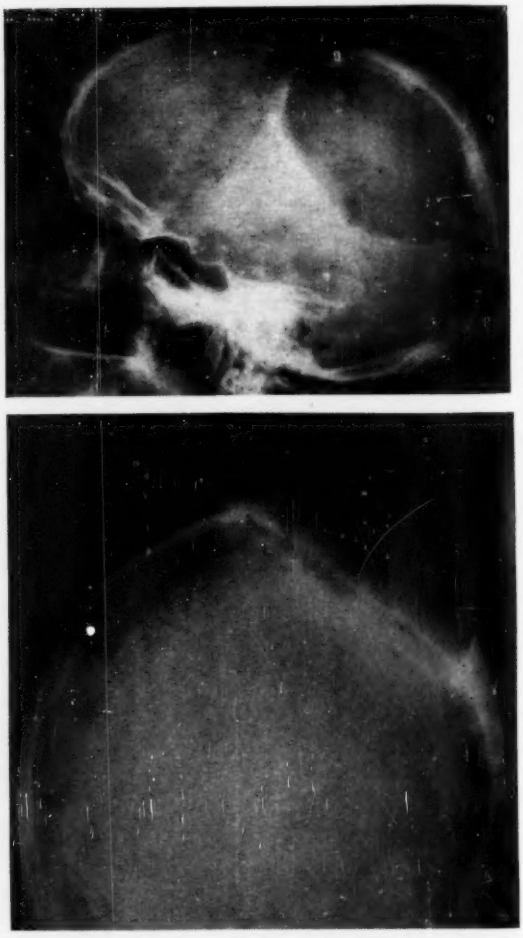


FIG. 10.—Skull radiographs showing a typical diploic pearly tumour. Note the smooth, thickened, bony margin. Some scalloping is present along with some suggestion of trabeculation.

had had epilepsy for 35 years. As a young man he had been struck on the vertex of the skull with a pickaxe and he began having convulsions soon thereafter. Examination revealed nothing of any significance apart from some tenderness in the right temporal region. Skull radiographs, however, revealed a circular defect in the right fronto-temporal region. Again, the edges were rounded and thickened, with a suggestion of scalloping, and a large area of calcification was seen in its centre.

A pearly tumour was found at operation that had eroded both tables of the skull and had extended through the dura to insinuate itself in the depths of the Sylvian fissure. As far as could be determined, the tumour was entirely removed and an acrylic cranioplasty was performed. There were no untoward events in his recovery, but unfortunately the epilepsy continues.

Histologically, both tumours were epidermoids.

Almost all of the examples of these intradiploic tumours recorded in the literature have been epidermoids (King, 1939; Mahoney, 1936; Rand and Reeves, 1943), although occasionally dermoids have been encountered (Schoen, 1939). Because of their slow growth, they may become tremendous and cause marked distortion of the underlying brain without producing much in the way of neurological signs (Horrax, Yorshis, and Lavine, 1935; King, 1939). The characteristic radiological changes are generally believed to be diagnostic.

Suprasellar.—Pearly tumours in the suprasellar region usually present as chiasmal syndromes of long duration. As a rule, endocrine changes are not evident (Findeisen and Tönnis, 1937; Floris and Castorina, 1950; Olivecrona, 1932; Rand and Reeves, 1943).

There are two examples in this series, both of them in women. One was 25 years of age, with visual symptoms for at least 11 years. She was completely blind in the left eye and had a temporal hemianopia in the right. There was optic atrophy bilaterally. She was obese, but there were no endocrine abnormalities.

The other was a 36-year-old woman, with visual symptoms for four years. She had a bitemporal hemianopia, with diminished visual acuity bilaterally. Primary optic atrophy was present in both eyes. Again no endocrine changes were found.

In both patients the cerebrospinal fluid protein was normal.

Skull radiographs revealed flattening of the dorsum sellae and posterior clinoid processes in one case. In the other, the sella turcica and the optic foramina were normal, but arteriograms demonstrated a suprasellar mass.

FIG. 11.—Microscopic section of the capsule of a suprasellar pearly tumour. There is a layer of stratified squamous epithelium without any trace of dermal elements. Inside the epidermal layer there are abundant amounts of laminated debris that make up the bulk of the tumour. (Haematoxylin and eosin × 268.)

At operation typical pearly tumours were found. In each instance the capsule was extremely thin and intimately associated with the various structures in this region, especially the optic nerves and internal carotid arteries. The interior of the tumours was removed and that part of the wall that would come away freely was excised. Total removal was not attempted, for fear of further damaging the optic nerves.

Unfortunately, no traces of the capsule could be found in one patient, although there was abundant amorphous flaky material in the histological sections. Sections of the capsule from the other patient revealed a layer of stratified squamous epithelium without any trace of dermal elements (Fig. 11).

In the first patient, vision improved considerably in the right eye and the temporal hemianopia disappeared. The left eye remained blind. She continues to do well from this standpoint five years post-operatively.

The other patient also improved, with a filling out of both visual fields, but recurrence may have taken place after seven years.

In 1932 Olivecrona presented two patients with similar lesions. In both cases the chiasmal syndrome predominated, with optic atrophy and visual field changes the main abnormal findings. Endocrine function was unimpaired.

He graphically described his operative findings, emphasizing the adherence of the capsule to vital structures, and advised against any attempt at its total removal. There is general agreement on this point (Findeisen and Tönnis, 1937; Rand and Reeves, 1943).

He mentioned radiological changes in the sellar region not encountered in the present series. These consisted of widening of one or both optic foramina and enlargement of the sulcus chiasmaticus. The sella turcica itself was intact. Findeisen and Tönnis (1937), on the other hand, described an example of sellar erosion in a suprasellar epidermoid. Suprasellar calcification in these tumours has also been reported (Floris and Castorina, 1950).

Endocrine abnormalities have been known to occur in association with suprasellar epidermoids. David, Lacroix, Thierry, and Brun (1936) described infantilism and undescended testes in an 11-year-old boy. Other examples have been recorded by de Martel and Guillaume (1938) and by Paleari (1939). It would appear from these reports that the " suprasellar epidermoid " was clearly distinguished from the more common Rathké pouch tumour.

Intracerebral.—Certain points about the intracerebral pearly tumours tend to differentiate them from other intracranial neoplasms. Epilepsy is often a presenting complaint and may exist as the only symptom for years before the onset of others. Signs of increased intracranial pressure are by no means a constant finding, and the cerebrospinal fluid protein is usually normal.

There were seven patients in this series with lesions of this nature (Table III). Epilepsy featured in the history of four of them. In one (Case 7) it was the only complaint. In three others (Cases 1, 5, and 6) it constituted the initial symptom and only terminally became associated with other complaints. A fifth patient (Case 4) had peculiar attacks of drowsiness, unassociated with convulsions, late in the illness. Epilepsy is known to have occurred in 41% of 138 cases of cerebral epidermoids and dermoids recorded in the literature.

Although most of the patients in this group had signs indicating the presence of an intracranial tumour, four of them had normal fundi, and indeed only 50% of 212 intracranial epidermoids and dermoids found in the literature were noted to have papilloedema. One of our patients (Case 5), with a 10-year-history of epilepsy, had no abnormal neurological findings. Increased cerebrospinal fluid pressure incited further investigations which revealed a huge epidermoid, 8-10 cm. in diameter, in the temporo-parietal region.

Pre-operative cerebrospinal fluid studies were available in five cases. In three of them the protein was well within normal limits. In the other two it was only slightly elevated. Among 58 cases in the literature in which the spinal fluid was examined there were only eight in which the protein content was increased, an incidence of 14%.

All of these patients were operated upon, and removal was thought to have been complete in four of them, although, as will appear later, it is often difficult to be certain that all portions of the capsule have been removed. One patient (Case 4) died two years post-operatively of unknown cause. After such a short interval it is unlikely to have been a recurrence. On the other hand, another patient (Case 2) died of recurrence 13 years after operation. There are no signs of recurrence in the others who

TABLE III

INTRACEREBRAL PEARLY TUMOURS

	Age	Sex	Duration of Symptoms (yr.)	Epilepsy	Papill-oedema	C.S.F. Protein (mg./100 ml.)	Post-operative Pleo-cytosis	Estimated Removal	Recur-rence	Years Followed
1. G.M. (London Hospital)	49	F	8	Yes	No	30	No	Complete	No	18
2. W.F. (St. Hugh's Hospital, Oxford)	29	M	3 mth.	No	Yes	35	Yes*	Incom-plete	Yes	Died of re-currence 13 years post-operatively
3. E.E. (St. Hugh's Hospital, Oxford)	24	F	6 mth.	No	Yes	65	No	Complete	No	13
4. D.A. (R.I. No. 51993/46)	30	F	2	Yes	No	—	Yes†	Complete	No	Died 2 years post-operatively
5. W.H. (R.I. No. 63934/46)	31	M	10	Yes	No	20	Yes	Complete	No	8
6. L.H. (R.I. No. 108193/49)	28	F	10	Yes	Yes	—	No	Incom-plete	No	6
7. D.W. (R.I. No. 197549)	29	M	8	Yes	Yes	60	No	Incom-plete	No	1

* Developed brain abscess, cultures remained sterile.

† Developed *Strep. viridans* meningitis post-operatively.

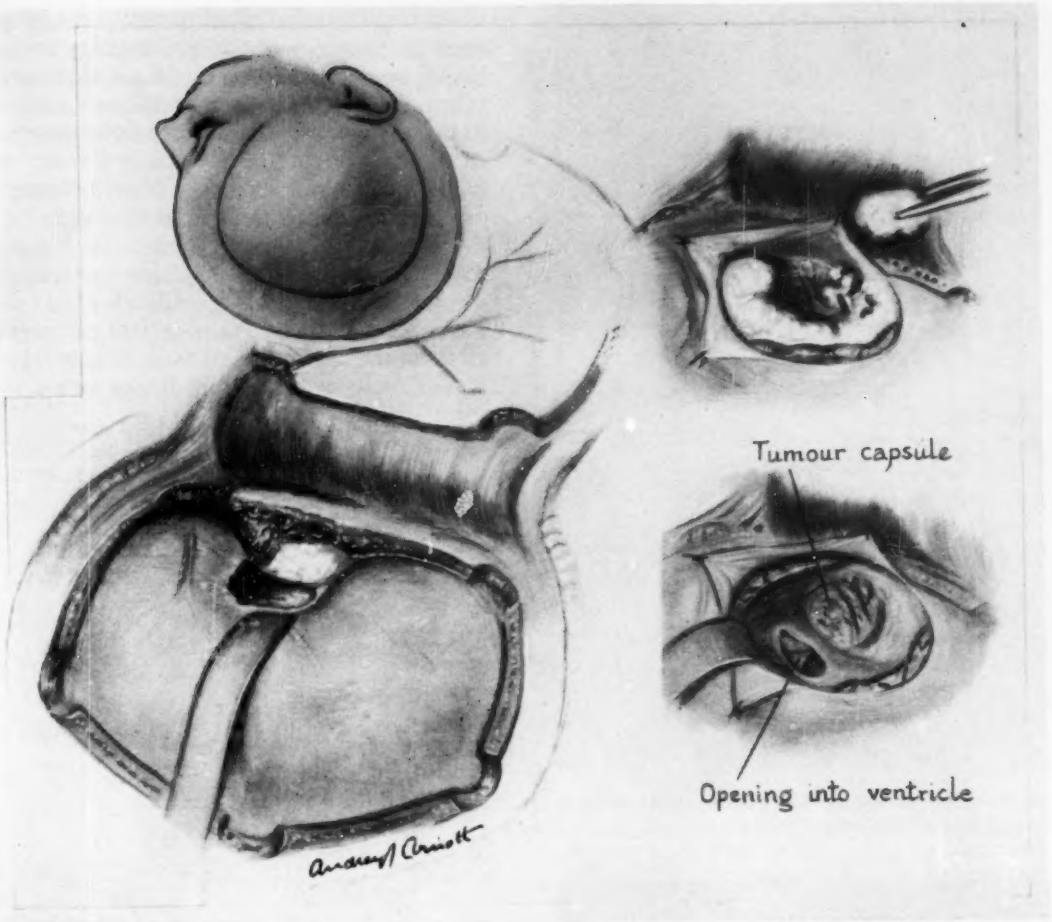


FIG. 12.—Operative drawing of an intracerebral pearly tumour (Case 4). It apparently arose from the temporal bone, penetrated the dura, and eventually extended into the temporal horn of the lateral ventricle.

have been followed for an average period of nine years. Histologically, all of these tumours were epidermoids.

In three of these patients the post-operative course was complicated by a persistent cerebrospinal fluid pleocytosis which prolonged their convalescence considerably.

The most characteristic feature of these lesions is their ventriculographic appearance. This is by virtue of their almost invariable relation to the subarachnoid space or lateral ventricles. In all of the patients in this series the tumour lay in direct relation to some part of the lateral ventricles. It was primarily intraventricular in five cases. In one case it seemed to extend into the ventricle from the subarachnoid space, and in another (Case 4) it arose from the temporal bone and extended into the temporal horn (Fig. 12).

Pre-operative air studies were performed in five patients and in each instance radiography revealed characteristic findings (Figs. 13 and 14). There are the usual signs of a space-occupying mass, but in addition scattered collections of air may be seen dispersed throughout the tumour, though on the whole more concentrated about its periphery. This cauliflower- or sponge-like appearance represents a lacework of communicating channels in the irregular grooves and clefts over the surface of the tumour, which may be thrown into deep folds.

These characteristics have been described previously and are generally agreed to be diagnostic (Childe and Young, 1947; Dyke and Davidoff, 1937; Weinberger, 1938).

Cerebello-pontine Angle.—The cerebello-pontine angle is not an unusual location for the epidermoid type of pearly tumours which must be differentiated from the more common acoustic neurinomas and meningiomas.

Three examples were found in this series (Table IV).

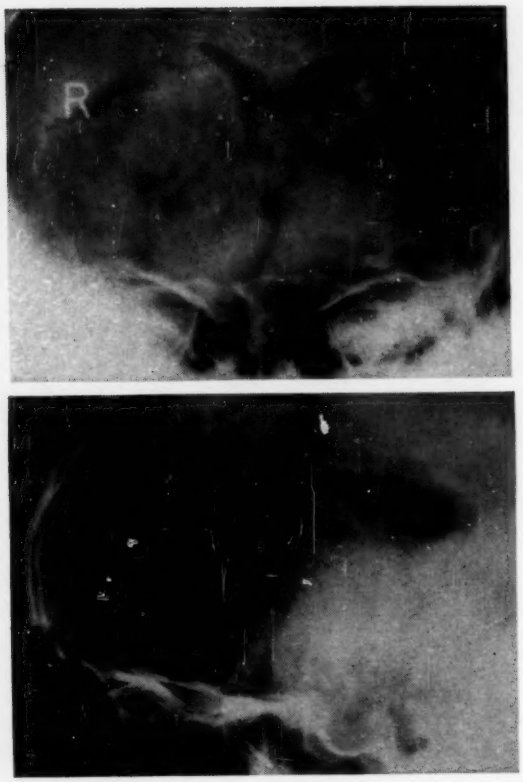


FIG. 13.—Encephalogram (Case 7). Pearly tumour in the right frontal region. (For description see text.)

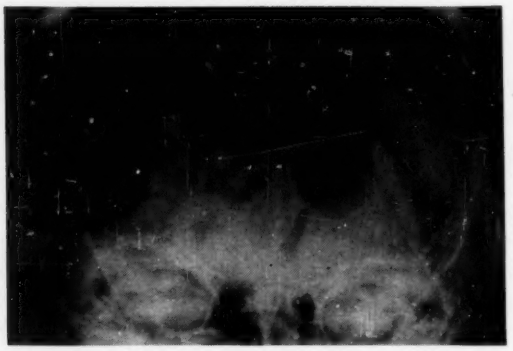


FIG. 14.—Ventriculogram (Case 5). Pearly tumour right fronto-temporal region. (For description see text.)

All had findings typical of tumours in this region, such as ataxia, with ipsilateral fifth, seventh, and eighth nerve involvement. In addition, one patient (Case 2) had a contralateral homonymous hemianopia which was found to result from an extension of the tumour through the incisura compressing the posterior cerebral artery. None of them presented with symptoms of trigeminal neuralgia, which has been described in other series (Gonzalez Revilla, 1947; Olivecrona, 1949). There was a long history of gradually increasing disability in all three. Papilloedema was present in two patients. In all of them the cerebrospinal fluid protein was normal. Radiographs of the petrous bones were also normal in each case.

At operation typical pearly tumours were found. Total removal was thought to have been accomplished in only one case, portions of the capsule having been left behind in the other two. All of the tumours were epidermoids (Fig. 15).

One patient died two months after operation of an aseptic meningitis and bronchopneumonia. Another has increasing ataxia eight years post-operatively which may represent incipient recurrence. The third patient, whose tumour was probably completely removed, is well six years post-operatively.

A normal cerebrospinal fluid protein concentration seems to be a characteristic of pearly tumours in this region. This was true in all of the cases in this group. Of the 49 examples of cerebello-pontine angle epidermoids found in the literature, there were 13 cases in which the cerebrospinal fluid findings were recorded. In 11 of these the protein was within normal limits. Findeisen and Tönnis (1937) described six examples of epidermoids in this location and remarked on the normal spinal fluid findings in five of them.

Although all three of the patients in this group were virtually totally deaf, with absent caloric responses on the involved side, other examples are recorded in which eighth nerve involvement was not evident. Olivecrona (1949) found that in five out of seven of his patients with cerebello-pontine angle "cholesteatomas" eighth nerve function was normal.

TABLE IV

CEREBELLO-PONTINE ANGLE PEARLY TUMOURS

	Age	Sex	Duration of Symptoms (yr.)	Papilloedema	C.S.F. Protein (mg./100 ml.)	Post-operative Pleocytosis	Follow-up
1. S.R. (London Hospital)	56	F	10	Yes	25	Yes	Died 2 mth. post-operatively
2. A.H. (R.I. No. 81380/47)	38	M	12	Yes	40	No	May be recurring 8 yr. post-operatively
3. V.V. (R.I. No. 130226)	37	F	8	No	52	No	No signs of recurrence 6 yr. post-operatively

Gonzalez Revilla (1948) found normal hearing in 10 out of 13 patients with this condition. In nine of them labyrinthine function was also unimpaired. Lewis and Echols (1951) described a patient whose hearing improved following removal of a tumour of this nature.

In patients presenting with a cerebello-pontine angle syndrome, a normal protein in the cerebrospinal fluid suggests the presence of a pearly tumour, although this sometimes occurs in meningiomas and very rarely in acoustic tumours. An intact eighth nerve on the affected side may be further evidence for this diagnosis.

Cerebellar.—Pearly tumours arising in the region of the cerebellum tend to lie in the midline, occupying the vermis and fourth ventricle. Histologically, the majority of these are dermoids and, as such, are frequently associated with other congenital anomalies (Logue and Till, 1952; Matson and Ingraham, 1951; Peyton and Baker, 1942).

Eight patients in this series had pearly tumours in this region (Table V). All of them lay in the midline, occupying the vermis or fourth ventricle. Only two of these lesions were epidermoids; the rest were dermoids.

Three of the patients with dermoids also had dermoids of the scalp, together with dermal sinuses. In addition, multiple fusion defects were noted in radiographs of the vertebral column of one patient.

In only three cases was papilloedema evident. Cerebrospinal fluid determinations were available in six cases, although in one they were complicated by the presence of meningitis. The protein level was elevated in three instances.

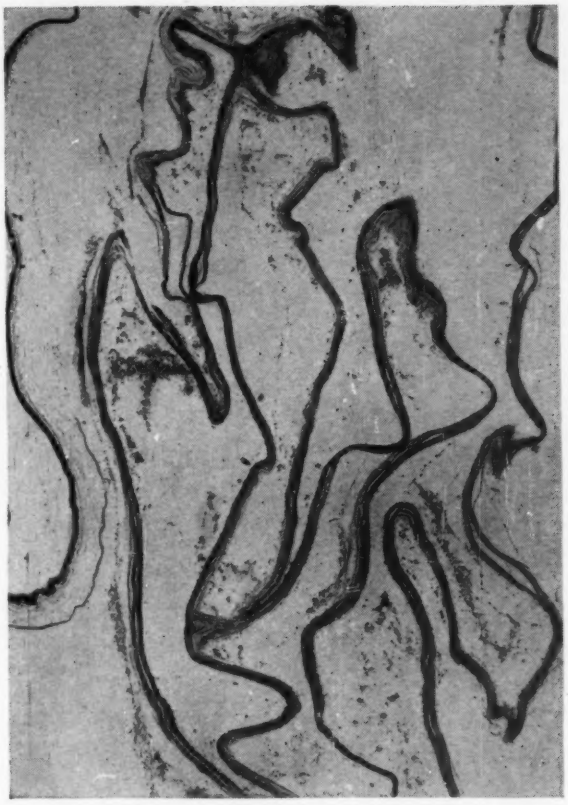


FIG. 15.—Microscopic section showing the tumour capsule in Case 3 of the cerebello-pontine angle group. The epidermal layer is extremely thin and in places is only one or two cells in thickness. No dermal elements are present. (Haematoxylin and eosin × 40.)

All of these patients had operations. Removal was believed to have been total in seven cases. Three

TABLE V
CEREBELLAR PEARLY TUMOURS

	Age	Sex	Other Anomalies	Papill-oedema	C.S.F. Protein (mg./100 ml.)	Estimated Removal	Type	C.S.F. Pleo-cytosis	Recur-rence	Years Followed
1. J.S. (London Hospital)	6	F	No	Yes	—	Complete	Dermoid	No	No	22
2. E.S. (R.I. No. 7560)	32	M	No	Yes	45	Complete	Epidermoid	Yes	No	16
3. E.D. (R.I. No. 97680/48)	55	F	No	No	65	Complete	Dermoid	Yes*	—	Died 5 weeks post-operatively
4. T.C. (R.I. No. 125415/50)	18	F	No	No	—	Complete	Dermoid	Yes	—	Died 24 hr. post-operatively
5. E.C. (R.I. No. 133140)	39	F	No	No	55	Complete	Epidermoid	Yes	No	5
6. C.D. (R.I. No. 153722)	3	M	Dermal sinus; dermoid scalp excised 6 mth. before	Yes	80	Complete	Dermoid	Admitted with menin-gitis†	—	Died 4 weeks post-operatively
7. S.R. (R.I. No. 160296)	5	F	Dermal sinus; dermoid scalp, fusion defects spine	No	125	Complete	Dermoid	Yes	No	4
8 C.N. (R.I.)	20	M	Dermoid scalp and dermal sinus excised at 5 years of age	No	70	Incom-plete	Dermoid	Yes‡	No	4

* Developed a Gram-achromobacter meningitis.
† Admitted with meningitis.
‡ Transient episode of meningismus three years post-operatively; cultures all sterile.

FIG. 16.—Encephalogram in a cerebellar pearly tumour (Case 5). The tumour can be seen projecting into a dilated fourth ventricle. (From Sheldon, Wickbom, and Pennybacker, 1953, by permission of the publishers.)

FIG. 17.—Occipital skull radiograph in a cerebellar dermoid (Case 6) showing the linear bony defect lying in the midline.

deaths occurred in the immediate post-operative period. There have been no signs of recurrence in those surviving.

Six patients had a prolonged cerebrospinal fluid pleocytosis post-operatively.

Clinically, these patients sometimes present as straightforward cerebellar tumours; on the other hand, they may present a very bizarre clinical picture.

One patient (Case 3) had signs and symptoms suggesting a spinal cord tumour, but she also had a seventh nerve palsy. At operation a dermoid was found involving the upper cervical cord and extending through the foramen magnum to lodge in the vermis and fourth ventricle. During the removal of this tumour some of its fragments spilled into the subarachnoid space. She developed a cerebrospinal fluid pleocytosis, but all the cultures remained sterile for one month. She then developed a Gram-negative Achromobacter meningitis and died four days later.

Another patient (Case 4) was thought to have disseminated sclerosis. She had complained of difficulty in swallowing and mild unsteadiness for two years intermittently. Ten days before admission her condition worsened, and she was admitted critically ill. In the absence of signs of increased intracranial pressure an encephalogram was performed, revealing a large posterior fossa tumour. After this her condition deteriorated to such an extent that immediate exploration was deemed necessary. At operation a large dermoid was found, occupying the vermis and fourth ventricle. Removal of this tumour was not particularly difficult, but she remained critically ill and died 24 hours post-operatively.

Case 5 presented as a cerebello-pontine angle syndrome, with ataxia and deafness associated with a fifth and seventh nerve involvement. An encephalogram was performed, however, which revealed a large tumour in the fourth ventricle that had an appearance highly suggestive of a pearly tumour (Fig. 16). At operation an epidermoid was found, occupying the fourth ventricle and extending through the foramen of Luschka. This was removed, and she remains fairly well five years after operation.

Of special importance are patients in this group with dermal sinuses, because of the risk of meningitis to which attention was called by Matson and Ingraham (1951). One (Case 6) was a 3-year-old child who had a small cyst in the occipital region that drained occasionally, and for two years he had had recurrent bouts of meningitis. Six months before admission this cyst had been excised. He was admitted suffering from a *B. coli* and alpha haemolytic streptococcus meningitis which proved

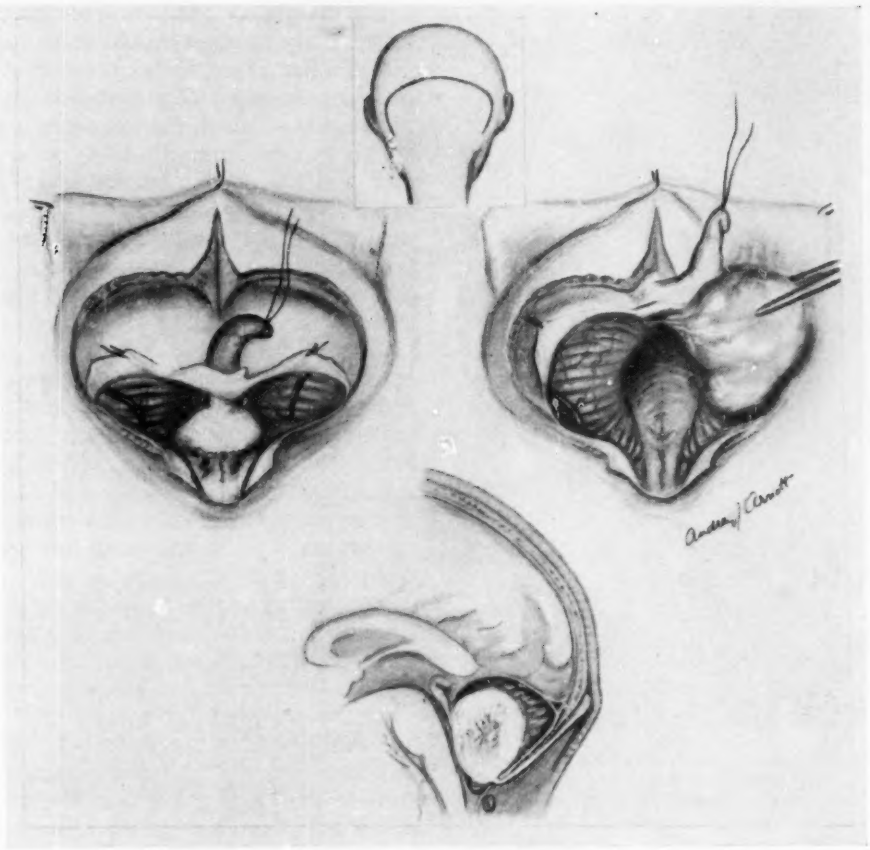


FIG. 18.—Operative drawing (Case 6 of the cerebellar group) showing the relations of the dermal sinus to the bony groove and to the cerebellar dermoid. (For description, see text.)

refractory to treatment. In addition to meningeal signs, his head was enlarged and he had bilateral papilloedema and bilateral sixth nerve palsies. There were no cerebellar signs. Skull radiographs revealed a midline groove in the occipital bone through which the deep attachments of the scalp dermoid had presumably extended (Fig. 17).

After three days of ventricular drainage, cerebellar exploration was carried out (Fig. 18). The sinus was identified, embedded in a groove in the occipital bone. No complete bony defect was found. It pierced the dura at the foramen magnum and, on exposing the cerebellum, was seen to enter a pinkish-white tumour occupying the greater part of the vermis and displacing both cerebellar hemispheres laterally. The tumour contained typical caseous material and a few hairs. It also contained pus, and the surrounding area was obviously infected.

The histological sections revealed a typical dermoid tumour with infiltration of the dermal layer by inflammatory cells (Fig. 19).

The child was given large doses of antibiotics after removal of the tumour, but he remained critically ill and died one month post-operatively.

Of the remaining patients with dermal sinuses one, a 5-year-old girl (Case 7), presented with a draining occipital sinus and signs of increased intracranial pressure. She had never had meningitis.

Skull radiographs revealed the same findings as noted before, a linear groove in the occipital bone (Fig. 20). In addition, there were multiple fusion defects throughout the whole of the vertebral column.

At operation a dermal sinus was found extending into a large mid-cerebellar dermoid. Removal was without event, and she remains well four years later.

The third patient, a 20-year-old man (Case 8), had had a scalp dermoid and dermal sinus excised at 5 years of age and a large posterior fossa dermoid subtotally removed three years before. He was admitted with a cerebrospinal fluid pleocytosis, presumably related to the remaining tumour, but this subsided with chemotherapy and further exploration was not called for.

FIG. 19.—Histological section of the tumour capsule in a cerebellar dermoid (Case 6). In addition to the epidermal layer, a dermal layer is also present containing hair follicles, fat, and connective tissue. Infiltration by inflammatory processes can also be seen. (Haematoxylin and eosin × 46.)

The main considerations in respect to the posterior fossa pearly tumours would seem to be twofold.

In the first place, early operation seems indicated, once the diagnosis of a posterior fossa tumour has been made. Two of the three post-operative deaths in this group (Cases 3 and 4) occurred in patients who had had symptoms for seven years and two years respectively. Total removal is often possible without undue hazard if the tumour has not become too extensive and if the patient's physical state has not been overwhelmed by the attendant neurological deficit.

Secondly, when patients present with meningitis of unexplained origin a careful search should be made for a congenital dermal sinus in the occipital region (or over the entire vertebral column, for that matter). These structures often extend epi- or sub-durally, where they may end as a blind pouch or they may terminate in a dermoid. If they are patent, an obvious entrance for infection exists. Occipital skull radiographs may also help by demonstrating a small midline bony defect or groove. Once the infection has been controlled, the sinus, together with its deep extension, can be removed without undue risk.

On the other hand, if these sinuses are discovered in patients without a history of meningitis, they should be excised to prevent such an occurrence, even in the absence of neurological signs. These points have been stressed by Matson and Ingraham

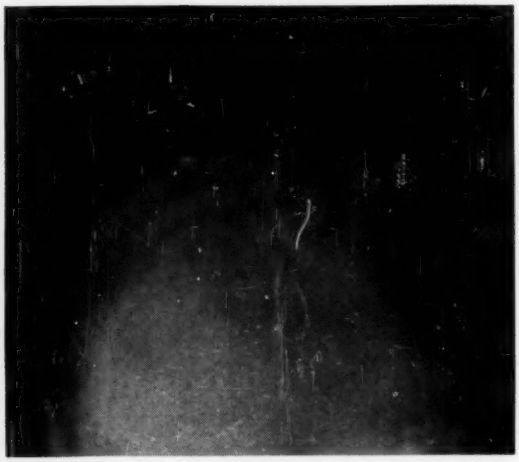


FIG. 20.—Occipital skull radiograph (Case 7 of the cerebellar group) showing another example of this linear groove. Note the separation of the sagittal suture.

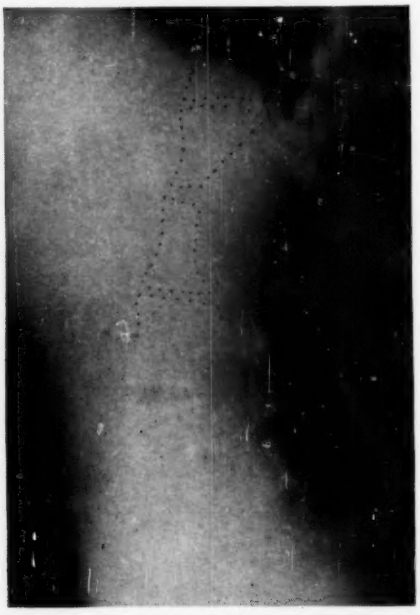


FIG. 21.—Spine radiograph (Case 4 of the intraspinal group). The erosion of the vertebral bodies is extensive. Note the thickened bony margins.

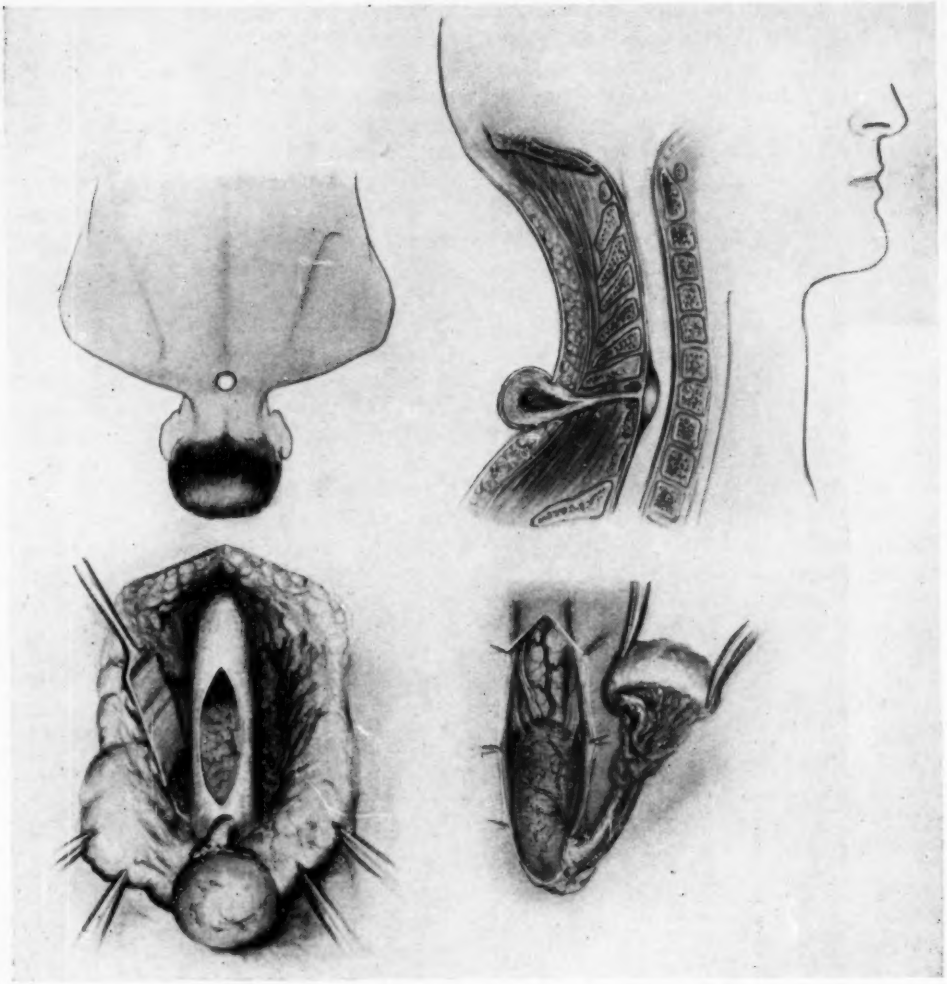


FIG. 22.—Drawing showing the relations of the tumour in Case 2 of the intraspinal group. The tumour was entirely extramedullary and was connected to a cutaneous dermoid through a sinus that extended through a bifid first thoracic vertebra.

(1951). They presented 10 patients who had congenital dermal sinuses with extensions into the posterior fossa. Meningitis was a primary feature in five of their cases. Two others had cerebellar abscesses, and one had osteomyelitis. Logue and Till (1952), in discussing the posterior fossa dermoids, described three cases having intradural dermoids with complete sinuses. Two of these patients had frank meningitis, and the third developed meningitis after excision of the sinus.

Intraspinal.—Although pearly tumours have been found at all levels of the spinal canal, they are considerably more common in its lower portion. In 1941 List collected all of the reported cases and found that 65% of these lesions were located below the twelfth dorsal vertebra. Dermoids are slightly more common in this location and, as in the occipital region, are frequently associated with other congenital anomalies, notably dermal sinuses. Sachs and Horrax (1949) reviewed this subject and found 61 cases of intraspinal dermoids and epidermoids in the literature. Of these at least 36 cases were dermoids. Of the 14 tumours associated with dermal sinuses, only one was an epidermoid. All the rest were dermoids.

Typically, either type may present as a cauda equina tumour, often becoming enormous and completely filling the spinal canal in that region. Spine radiographs may show widening of the interpeduncular space, or erosion of the pedicles themselves. Lateral views often show erosion of the posterior surfaces of the bodies (Fig. 21).

Seven patients in this series had intraspinal pearly tumours (Table VI). In all instances the tumour lay

intradurally. It was extramedullary in two cases (Cases 1 and 3) and entirely intramedullary in two others (Cases 2 and 5). In the remaining three patients the bulk of the tumour mass lay enmeshed in the cauda equina, but its superior portion extended into the conus medullaris to become more or less continuous with it.

Histologically, there were two epidermoids in this group. The others were dermoids, three of which were associated with other anomalies, such as dermal sinus and spina bifida.

The protein content of the spinal fluid was not invariably elevated in these cases, although higher determinations were found in the intraspinal tumours compared with those located elsewhere. This was also true in other reported series and may be related to the degree and duration of spinal block.

When these tumours are intricately involved in the cauda equina, or when they invade the spinal cord itself, complete removal may be impossible without damaging these structures. They tend to recur extremely slowly, in spite of their confined location. Although operative removal was known to have been incomplete in four patients, there has been known recurrence in only one instance (Case 6) four years, and again five years, after the first operation. There have been no signs of recurrence in any of the others followed for an average of eight years.

As mentioned before, three patients had spinal dermoids in association with other congenital abnormalities. Two of these had dermal sinuses. In one, a 40-year-old man (Case 3), it began in a cutaneous mass and extended into the intradural space through a spina bifida at the first thoracic vertebra. It terminated in a dermoid which lay over the posterior surface of the spinal cord (Fig. 22). This tumour lay entirely extramedullary and was believed to have been totally removed.

The other patient, an infant (Case 7), had a small cutaneous sinus in the upper sacral region that extended intradurally through a bifid second sacral vertebra into a large cauda equina dermoid. He presented as a staphylococcus aureus meningitis. Histological sections of this growth revealed it to be a dermoid, obviously infected, with a marked

Table VI
SPINAL PEARLY TUMOURS

	Age	Sex	Location	Other Anomalies	Spinal Block	C.S.F. Protein (mg./100 ml.)	Estimated Removal	Type	Recurrence	Years Followed
1. J.C.W. (R.I. No. 2410)	18	F	Intradural at L2	Yes	Yes	310	Complete	Dermoid	No	18
2. A.C. (R.I. No. 6824)	32	M	Intramedullary at T3	No	Yes	35	Complete	Epidermoid	No	16
3. N.B. (R.I. No. 10818)	40	M	Extramedullary at T1	Yes	No	48	Incomplete	Dermoid	No	11
4. E.G. (R.I. No. 18089)	20	F	Intramedullary and extramedullary L1, L2	No	No	70	Complete	Dermoid	No	15
5. T.W. (R.I. No. 4373/43)	26	M	Intramedullary T12	No	No	70	Incomplete	Dermoid	No	13
6. J.P.R. (R.I. No. 77234/47)	15	F	Intramedullary and extramedullary L1 to L3	No	No	1,000	Incomplete	Epidermoid	Yes*	8
7. M.A. (R.I. No. 209169)	6 mth.	M	Intramedullary and extramedullary T11 to S2	Yes	No	80†	Incomplete	Dermoid	No	1

* Recurrence four years and five years after first operation but no recurrence two years later.
† Admitted with *Staph. aureus* meningitis.

Table VII
ASEPTIC MENINGITIS IN INTRADURAL PEARLY TUMOURS

	No of Cases	C.S.F. Pleocytosis	Culture	Culture of Tumour
Suprasellar	2	0	—	1 Pyocyaneus
Intracerebral	7	3	1 (*Strep. viridans*)	2 *Strep. viridans* and haemolytic strep.
Cerebello-pontine angle	3	1	No	0
Mid-cerebellar	8	6	1 Gram-negative Achromobacter	0
Intraspinal	7	0	—	0
Total	27	10	2	3

FIG. 23.—Microscopic section of a spinal dermoid (Case 7). There is an extensive inflammatory cell reaction in the dermal layer and a portion of the epidermis has been destroyed. (Haematoxylin and eosin × 46.)

white cell infiltration of the dermis that destroyed a portion of the epidermal layer (Fig. 23).

These cases are often first seen because of meningitis, at which time there may not be any signs of spinal cord or cauda equina involvement. They are similar to those patients with occipital dermal sinuses and should be treated accordingly (Kahn, Bassett, Schneider, and Crosby, 1955; Walker and Bucy, 1934).

Comment

In the surgical treatment of the pearly tumours two main problems arise. The first is the occurrence of cerebrospinal fluid pleocytosis or aseptic meningitis during the post-operative period. The second is the question of recurrence.

Aseptic meningitis is a frequent post-operative complication, especially if some of the tumour is left behind. It may persist for weeks and, except for the absence of micro-organisms, the spinal fluid closely resembles that of acute purulent meningitis. There are numerous reports attesting this fact (Bailey, 1920; Critchley and Ferguson, 1928; Grant and Austin, 1950; Mahoney, 1936; Olivecrona, 1932; Peyton and Baker, 1942). It may remain sterile and subside spontaneously, or it may develop into a bacterial meningitis and, as a matter of fact, cultures taken from pearly tumours at the time of operation occasionally grow pathogenic organisms.

Out of 27 cases of intradural epidermoids and dermoids in the present series, 10 developed a cerebrospinal fluid pleocytosis post-operatively (Table VII). Repeated cultures were sterile in eight patients. In one of these (Case 2 of the intracerebral group) the process persisted and eventually a sterile brain abscess occurred which required re-exploration. In two patients a bacterial meningitis developed. In such cases the appearance of organisms may be due either to their delayed growth on culture or to their introduction at lumbar puncture. One patient died four days later. In the other, the process eventually resolved with antibiotic treatment.

In five cases, exclusive of those presenting with meningitis, micro-organisms were cultured from the tumour at the time of operation. One of the growths arose in the petrous bone, however, and might possibly have been related to a chronic middle ear infection. One positive culture was obtained from an orbital dermoid. It is possible, of course, that all five cultures may have been due to contaminants.

Examples of aseptic meningitis resulting from spontaneous leakage of these tumours have been reported (Bauditz, 1933; Essellier, 1945; Lehoczky, 1951). Bauditz (1933) cites three cases in which the cyst contents were found by lumbar puncture after leakage had occurred.

Cholesterin has been incriminated as the inciting cause of aseptic meningitis. Greenfield (1932) believes that it plays an important role in producing the pleocytosis occurring a few days after subarachnoid haemorrhage. He cites the experimental work of Bender, who in 1925 injected various lipoidal fractions obtained from myelin into the subarachnoid space of animals and found that cholesterin produced a much more intense reaction than did the other fractions. This irritating action of cholesterin is also demonstrated by the presence of a foreign body giant cell reaction around cholesterol crystals (Fig. 24).

Bauditz (1933) discussed a case in which a basal dermoid ruptured spontaneously, causing death. Histological sections of the brain revealed numerous giant cells in the ventricular system and subarachnoid space, along with an intense glial reaction. Mahoney (1936) obtained similar findings by injecting cholesterine crystals into the cerebral cortex of dogs.

In an attempt to prevent this complication care should be taken at operation to avoid, as much as possible, contamination of the surrounding region by tumour contents. In this hospital prophylactic

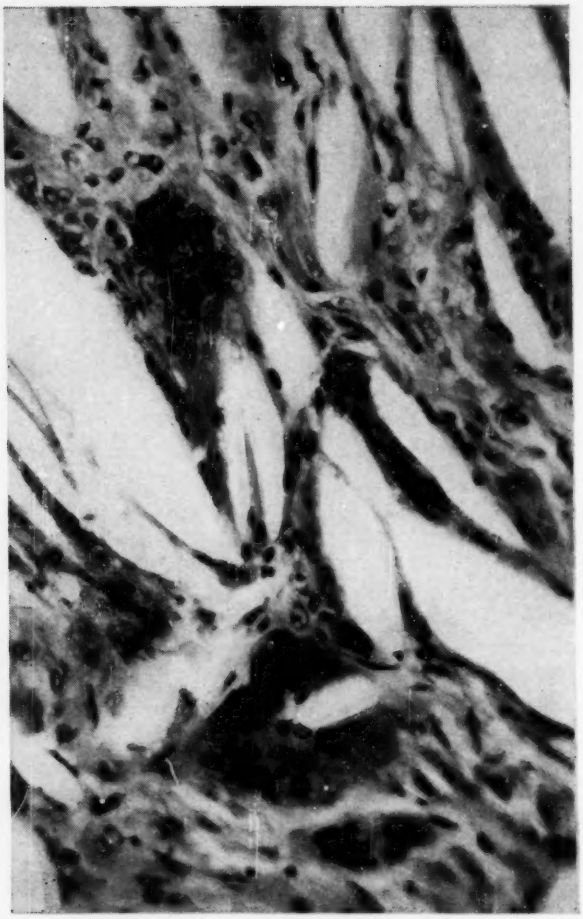


FIG. 24.—Microscopic section of the tumour wall in an epidermoid (Case 5 of the cerebellar group). The clear, cleft-like spaces represent cholesterol crystals that have dissolved out during processing. Many foreign body giant cells can be seen around these spaces. (Haematoxylin and eosin × 302.)

chemotherapy is given for several days after operation. Specimens of the tumour are taken for culture and sensitivity studies. If these are positive the appropriate antibiotic is used.

That these tumours recur following incomplete removal is well known. The capsule constitutes the only living part, and if remnants are left behind growth will continue (Bailey, 1920). However, these lesions are slow-growing, and years may pass before this becomes clinically evident. Sachs (1936) mentioned recurrence in a cerebello-pontine epidermoid 13 years after operation.

Of the 27 intradural tumours in this series removal was believed to have been incomplete in 12 cases. One patient (Case 2) of the intracerebral group died of recurrence 13 years after operation. Recurrence has also taken place in another patient (Case 6) of the spinal group four years and again five years after the first operation. One patient (Case 2 of the cerebello-pontine angle group) may be showing signs of recurrence after eight years, and one of the suprasellar group has shown signs of visual field changes seven years after operation. Recurrence is not known to have occurred in any of the others who have been followed for an average of about eight years. Removal was believed to have been complete in the remaining cases, and thus far none has recurred.

Total removal should be possible in the majority of extradural tumours without damaging vital structures, and every attempt should be made to do so.

In the intradural group, on the other hand, a different situation exists. The capsule may be densely adherent, or may actually invade vital structures. This is especially true in the suprasellar, cerebello-pontine angle, and intraspinal groups. If this is so, the tumour contents should be removed and portions of the capsule that come away easily should be excised. Parts adherent to major vessels, or functional nervous tissue, are best left behind.

Summary and Conclusions

A series is presented of 41 cases of pearly tumours related to the central nervous system. This term includes epidermoids and dermoids, since, in spite of their difference histologically, their characteristics are quite similar.

Two patients had pericranial dermoids unassociated with neurological abnormalities. Their aetiology is discussed along with their differentiation from encephalocele.

Six patients had orbital pearly tumours, with proptosis as the main complaint. Visual disturbances were minimal. The main indication for surgical removal of these growths is a cosmetic one, and good results may be obtained.

Six patients had pearly tumours arising in the petrous bone and presented with peripheral facial weakness, associated with deafness in five cases. Four had operations, but improved facial nerve function occurred in only one patient. Earlier operation should improve these results.

The features of the diploic pearly tumours are discussed, notably their characteristic radiological appearance. Two examples are cited.

Two patients had pearly tumours arising in the suprasellar region and presented with a chiasmal syndrome unassociated with endocrine abnormalities. Radiographs of the sella turcica were normal, except for some flattening of the posterior clinoid processes that may not be significant. Total removal of these tumours is hazardous because of their relation to the optic nerves and internal carotid

arteries. Intracapsular removal is probably preferable, since they recur so slowly.

Seven patients had intracerebral pearly tumours. Epilepsy featured in the history of four of them and may be a prominent characteristic in these cases. The diagnostic significance of air studies in these patients is discussed.

Three patients had cerebello-pontine angle epidermoids and presented with the usual features of tumours in this region. All had normal cerebrospinal fluid proteins, a finding significant in differentiating these tumours from acoustic neurinomas and cerebello-pontine angle meningiomas.

Eight patients had pearly tumours arising in the vermis and fourth ventricle. Three of them had associated dermal sinuses. Their role in the production of meningitis is emphasized, along with the importance of early surgical intervention in all of these cases.

Seven patients had intraspinal (intradural) pearly tumours. Six of them were at least in part intramedullary. Associated dermal sinuses were present in two patients, one of whom presented as a meningitis. When these growths are entangled in the cauda equina, or when they invade the spinal cord, incomplete removal seems advisable to prevent further damage to these structures.

All of the patients with extradural pearly tumours survived operation, and to our knowledge there have been no recurrences in this group.

Of the 27 patients with intradural tumours four died in the immediate post-operative period, a mortality of 15%. Three of these deaths occurred in patients in the cerebellar group and were attributed, at least in part, to late surgical intervention. The other occurred in a patient with a cerebello-pontine angle epidermoid.

Aseptic meningitis occurred in 10 patients with intradural pearly tumours. Repeated spinal fluid cultures were sterile in eight cases, although one of them later developed a sterile brain abscess requiring re-exploration. Two patients developed a bacterial meningitis, which was fatal in one of them. This complication is discussed, with reference to other recorded examples.

Recurrence is discussed in reference to the intradural group. Although removal was incomplete in at least 12 patients, known recurrence has taken place in only two of them, four and 13 years post-operatively. Two other patients may be showing signs of recurrence eight and seven years after operation. The remaining patients in this group have been followed for an average of eight years.

We wish to acknowledge our gratitude to Dr. Peter Daniel and Dr. Sabina Strich, of the Department of Neuropathology, for their help and advice concerning the pathology of these tumours together with the photomicrographs which were produced in their department, and to Dr. Philip Sheldon, of the Department of Radiology, who was instrumental in selecting the radiographs reproduced above. We are also indebted to Mrs. Joyce Gilbert for her help in gathering literature and preparing the manuscript.

REFERENCES*

Bailey, P. (1920). *Surg. Gynec. Obstet.*, **31**, 390.
—— (1924). *Arch. Surg.* (*Chicago*), **8**, 524.
Bauditz, A. (1933). *Z. ges. Neurol. Psychiat.* (*Orig.*), **144**, 135.
Bostroem, E. (1897). *Zbl. allg. Path. path. Anat.*, **8**, 1.
Brock, S., and Klenke, D. A. (1931). *Bull. neurol. Inst., N.Y.*, **1**, 328.
Childe, A. E., and Young, A. W. (1947). *Radiology*, **48**, 56.
Critchley, M., and Ferguson, F. R. (1928). *Brain*, **51**, 334.
Cruveilhier, J. (1829). *Anatomie Pathologique du Corps Humain*, Vol. I, Book 2, Plate 6. Baillière, Paris.
David, M., Lacroix, A., Thierry, S., and Brun, M. (1936). *Rev. neurol.* (*Paris*), **65**, 379.
Dyke, C. G., and Davidoff, L. M. (1937). *Bull. neurol. Inst., N.Y.*, **6**, 489.
Ernst, P. (1912). *Verh. dtsch. path. Ges.*, **15**, 226.
Essellier, A. (1945). *Schweiz. Z. allg. Path. Bakt.*, **8**, 41.
Findeisen, L., and Tönnis, W. (1937). *Zbl. Neurochir.*, **2**, 301.
Floris, V., and Castorina, G. (1950). *Riv. Neurol.*, **20**, 303.
Gonzalez Revilla, A. (1947). *J. Neurosurg.*, **4**, 233.
—— (1948). *Bull. Johns Hopk. Hosp.*, **83**, 187.
Grant, F. C., and Austin, G. M. (1950). *J. Neurosurg.*, **7**, 190.
Greenfield, J. G. (1932). In *Cytology and Cellular Pathology of the Nervous System*, ed. W. Penfield, Vol. 3, p. 1224. Hoeber, New York.
Harvey, S. C., and Burr, H. S. (1926). *Arch. Neurol. Psychiat.* (*Chicago*), **15**, 545.
Horrax, G. (1922). *Ibid.*, **8**, 265.
——, Yorshis, M., and Lavine, G. R. (1935). *Ibid.*, **33**, 1058.
Hug, O. (1942). *Virchows Arch. path. Anat.*, **308**, 679.
Jefferson, G., and Smalley, A. A. (1938). *J. Laryng.*, **53**, 417.
Kahn, E. A., Bassett, R. C., Schneider, R. C., and Crosby, E. C. (1955). *Correlative Neurosurgery*, p. 380. Thomas, Springfield, Ill.
King, J. E. J. (1939). *Ann. Surg.*, **109**, 649.
Körner (1900). *Z. Ohrenheilk.*, **37**, 352. Cited by Rosenwasser.
Lehoczky, T. de (1951). *Acta neurol. psychiat. belg.*, **51**, 319.
Lewis, M. L., and Echols, D. H. (1951). *Laryngoscope* (*St. Louis*), **61**, 1123.
List, C. F. (1941). *Surg. Gynec. Obstet.*, **73**, 525.
Logue, V., and Till, K. (1952). *Journal of Neurology, Neurosurgery and Psychiatry*, **15**, 1.
Love, J. G., and Kernohan, J. W. (1936). *J. Amer. med. Ass.*, **107**, 1876.
Mahoney, W. (1936). *Z. ges. Neurol. Psychiat.* (*Orig.*), **155**, 416.
Martel, T. de, and Guillaume, J. (1938). *Rev. Neurol.* (*Paris*), **69**, 384.
Matson, D. D., and Ingraham, F. D. (1951). *Pediatrics*, **8**, 463.
Montgomery, G. L., and Finlayson, D. I. C. (1934). *Brain*, **57**, 177.
Müller, J. (1838). *Ueber den feinern Bau und die Formen der krankhaften Geschwulste*. Reimer, Berlin.
Olivecrona, H. (1932). *Brain*, **55**, 122.
—— (1949). *Acta Psychiat.* (*Kbh.*), **24**, 639.
Paleari, A. (1939). *Riv. Neurol.*, **12**, 185.
Pennybacker, J. (1944). *Brit. J. Surg.*, **32**, 75.
Peyton, W. T., and Baker, A. B. (1942). *Arch. Neurol. Psychiat.* (*Chicago*), **47**, 890.
Rand, C. W., and Reeves, D. L. (1943). *Arch. Surg.* (*Chicago*), **46**, 350.
Raskin, N. (1949). *J. Neurosurg.*, **6**, 534.
Remak, von (1854). Cited by Critchley and Ferguson, p. 337.
Rosenwasser, H. (1935). *J. Mt Sinai Hosp.*, **2**, 56.
Sachs, E. (1936). In discussion, see Love, J. G. and Kernohan, J. W., p. 1883.
——, Jr., and Horrax, G. (1949). *J. Neurosurg.*, **6**, 97.
Schoen, H. (1939). *Röntgenpraxis*, **11**, 62.
Sheldon, P. W. E., Wickbom, I., and Pennybacker, J. B. (1953). *J. Fac. Radiol.* (*Lond.*), **4**, 275.
Simpson, R. R. (1954). *Proc. roy. Soc. Med.*, **47**, 205.
Stromeyer, F. (1909). *Beitr. path. Anat.*, **47**, 392.
Verattus (1745). Cited by Critchley and Ferguson, *q.v.* (1928).
Virchow, R. (1855). *Virchows Arch. path. Anat.*, **8**, 371.
Walker, A. E., and Bucy, P. C. (1934). *Brain*, **57**, 401.
Weinberger, L. M. (1938). *J. Mt Sinai Hosp.*, **5**, 565.

* Copies of a more complete bibliography are available on application to either of the authors.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 260.

PHYSIOLOGICAL TREMOR

BY

JOHN MARSHALL AND E. GEOFFREY WALSH

From the Neurological Unit, Northern General Hospital, and Department of Physiology, University of Edinburgh

Rhythmicity during muscular contration has long been studied. The earliest observations dealt with the sounds that can be heard on listening to a contracting muscle and were naturally limited by the poor sensitivity of the ear at low frequencies. When, in the second half of the nineteenth century, graphic recording techniques became readily available a number of papers were published dealing with the periodicity that can be recorded in myograms. Of outstanding interest were the findings of Schäfer (1886) who observed that

> " The curve of a voluntary muscular contraction . . . invariably shows, both at the commencement of the contraction and during its continuance, a series of undulations which succeed one another with almost exact regularity, and can, as it would seem, only be interpreted to indicate the rhythm of the muscular response to the voluntary stimuli which provoke the contraction. . . . The undulations . . . are plainly visible and are sufficiently regular in size and succession to leave no doubt in the mind of any person who has seen a graphic record of muscular tetanic contraction produced by exciting the nerve about 10 times in the second that the curve . . . is that of a similar contraction."

Schäfer did not discuss the natural periodicity of his recording system and his results were regarded as artefacts by Haycraft (1890). Nevertheless, other authors using different apparatus obtained somewhat similar results. As Schäfer's observations, if valid, might be expected to throw light on the organization of voluntary movements, it seemed important to see whether his results could be verified using apparatus which would give a faithful record of movement. The observations to be reported confirmed in large measure the facts reported by Schäfer. It then became necessary to enquire as to the origin of the rhythmicity. Horsley and Schäfer (1886) had found that a similar 10 c./sec. rhythm was present in graphic records of the movements of monkeys following stimulation of the motor cortex, and descending motor pathways at various frequencies. They stated:

> " We have found in nearly all cases that whatever the rate of excitation employed, provided it was not allowed to fall below a certain limit, the frequency of muscular response to stimulation of the cortex, as indicated by the undulations described by the myograph lever, does not vary with the rate of excitation, but maintains a nearly uniform rate of about 10 per second."

They concluded that the rhythmicity was determined at a spinal rather than at a cortical level.

With the discovery of the alpha waves of the electro-encephalogram the view has sometimes been advanced that physiological tremor of muscles is dependent upon impulses descending from the cerebral cortex at a rate of 10 c./sec. Since Horsley and Schäfer's observations appear directly opposed to this view we have attempted to determine the neurological level responsible for physiological tremor.

Methods

Most of the observations reported in this paper have been concerned with acceleration rather than displacement. The measurement of acceleration is advantageous for three reasons. First, the application of Newton's second law indicates that the force put into a limb will be reflected in its acceleration. Secondly, graphic records of acceleration reveal smaller discontinuities during the course of a movement than could be detected by comparable recording of displacement. Thirdly, the technique is simple and versatile.

An accelerometer double diode (Mullard DDR 100) was attached to a part of the limb under investigation. The anodes of such a valve are deflected by acceleration in one plane. Movement of the valve upset the balance of a bridge circuit, and the electrical output was fed through an Ediswan electro-encephalographic amplifier to both an ink-writer and an oscillograph.

The natural period of the accelerometer valve was 1,000 c./sec., and it may be regarded as accurately recording motion having sinusoidal components up to 250 c./sec. (manufacturer's figures). The response of the ink-writer was more limited; signals higher in frequency than 90 c./sec. would be seriously attenuated.

In order to ensure that the ink-writers on which the bulk of the recordings were to be made were able satisfactorily to follow the movements which we were likely to encounter, over 100 oscilloscope recordings were

photographed and studied. These comprised a wide variety of normal and abnormal movements. We were satisfied, as a result of these observations, that the ink-writers gave faithful records. This claim requires qualification. Owing to the use of a condenser coupled electro-encephalographic amplifier very slow accelerations were not recorded. The time constants used were 0·3 and 1·0 second. Because of this a movement may sometimes be recorded as an acceleration in one direction without the complementary swing of the record to the other side of the baseline corresponding to the phase of deceleration. This peculiarity does not affect the recording of the more rapid fluctuations with which this study has been concerned. Finally, it should be noted that a device of this nature is inevitably sensitive to centrifugal force and to gravity. Accordingly, since rotation was not restricted, and was inevitable in some of the movements studied, the potential records do not represent solely linear acceleration. These complications do not interfere with the purposes of the study, but the calibration in terms of " g " is meaningful only when the excursions are small, as in the maintenance of a posture.

The apparatus was calibrated by fixing the valve in a block of wood that fell in guides. An accelerometer falling freely produces a signal of constant amplitude but, because of the time constant of the amplifier, the record showed instead an exponentially decaying response. This was interrupted irregularly as the block of wood in falling ricocheted along the guides. In spite of this the determinations can be regarded as reliable for measurements of the distance travelled in a given time corresponded closely with the calculated values.

To dissect movement further, apparatus was used that was sensitive to the rate of acceleration, the fourth derivative of displacement. The transducer was a piezo-electric crystal, taken from a Brush headphone to which was cemented a small aluminium pellet to act as a mass. The input impedance of the attenuator with which the crystal was connected was 700,000 ohms and the time constant of the combination was 0·03 sec., a value short compared with the periodicity of the movements that were investigated. The crystal was almost critically damped, and its natural period was 60 c./sec. Such a device is inevitably sensitive to twisting as well as to linear motion. The currents produced by the crystal were recorded with standard electro-encephalographic apparatus, using an ink-writing pen. The device and the recorder cannot be regarded as displaying the fourth differential of position with great precision, but it is believed that the inaccuracies that may have been introduced have not given rise to misleading interpretations. For calibration the transducer was attached to a pendulum. The amplitude of the deflections that were observed when the swing was a known amplitude, together with a knowledge of the periodicity of the device, allowed an appropriate calibration to be performed.

Results

Effect of Rate of Movement and Recording Site v. Frequency of Physiological Tremor in Normal Adults.—The type of record may be illustrated in the first instance by those obtained when the accelerometer valve is held in the hand, and the wrist alternately flexed and extended. Movements of this kind when performed rapidly produce swings of the tracing which may for part of their course be smooth in contour. It is frequently noted, however, that superimposed upon the large swings of the baseline there is a series of oscillations of about 10 c./sec. If a series of movements is made it is found that the prominence of the 10 c./sec. rhythm increases, and the size of the baseline swing decreases the slower the movement. Eventually the movement breaks up into a series of discontinuities at 7 to 13 c./sec. (Fig. 1). The waves are quasi-sinusoidal. They constantly vary in shape, in duration, and in amplitude. No two movements will produce identical records. The size of the waves varies considerably in different people, and in the same person from time to time. A large change in the rate at which the movement is performed is liable to alter the amplitude but not the frequency of the waves. Faster components in the record may often be recognized by using high amplification and a fast (6 cm./sec.) paper speed. These features have always been inconspicuous and we have paid little attention to them. At no time did a rhythmic discharge at 50 c./sec. clearly manifest itself. Such a " Piper " rhythm might have been expected, for with powerful contractions the electromyogram gives evidence of synchronization at this frequency. Occasionally, however, short but well defined bursts of activity were recorded with a frequency of 15 to 20 c./sec.

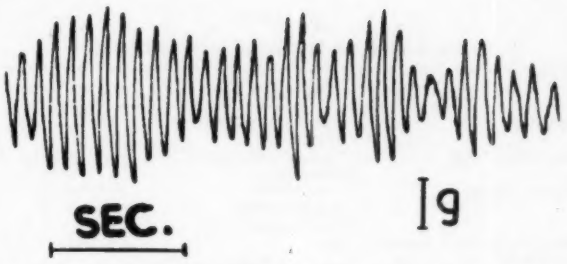


FIG. 1.—Tracing of wrist flexion and extension in a normal adult showing prominent 10 c./sec. rhythm.

On investigating the tremor in normal adults it was found that the frequency of the oscillations was much the same at a number of different sites. Thus activity at 7 to 12 c./sec. was seen at the wrist, elbow, shoulder, ankle, knee, and hip. Other workers also have recorded similar discontinuities in graphic records taken from a number of sites (Table I). Often the tremor may be found when the part of the body under investigation is merely resisting gravity, but sometimes it may be clearly recordable only during the course of a movement.

TABLE I
FREQUENCY OF TREMOR AND LOCATION

Authors	Recording Site	Frequency of Tremor
Schäfer (1886)	Opponens pollicis	10/sec.
	Biceps	10/sec.
Griffiths (1888)	Thenar eminence	10-15½/sec.
	Biceps	14/18/sec.
Harris (1894)	Tongue	10-15/sec.
	Neck muscles	12/sec.
	Thenar eminence	12/sec.
Ditchburn and Ginsborg (1953)	Eye	30-80/sec.
Eliasson and Gisselsson (1955)	Tensor tympani	10-20/sec.

The waves were on a number of occasions noted to be of greater amplitude when the limb was being lowered than when it was being raised at about the same rate. To check this point further a small weight was caused to oscillate up and down in a sinusoidal fashion, being carried on a string attached to a motor-driven pulley. The person followed the weight with his upper limb, keeping his finger level with the weight. Some control, therefore, was possible over the rate at which the arm was raised and lowered. It was possible to find a velocity at which tremor waves were seen readily on the curve corresponding to the descent whilst the ascent was smooth (Fig. 2). It may be remembered that when a limb is lowered active units are being stretched, a condition in which the twitch tension is increased (Hill, 1949).

Effect of Load upon the Tremor.—The effect of loading the limb was investigated. If a weight was placed upon the hand during movement of the wrist the rhythm often became less in amplitude, but again changed little in frequency. On the other hand, with the shoulder the application of weight often made the tremor waves more prominent; again, however, they did not appear to alter in frequency (Fig. 3).

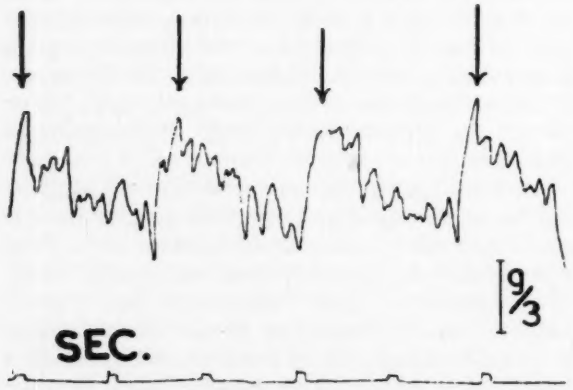


FIG. 2.—Record of hand following a weight moving up and down in a sinusoidal fashion, the top of the excursion being marked by an arrow. Ascent is smooth; descent shows slow tremor waves.

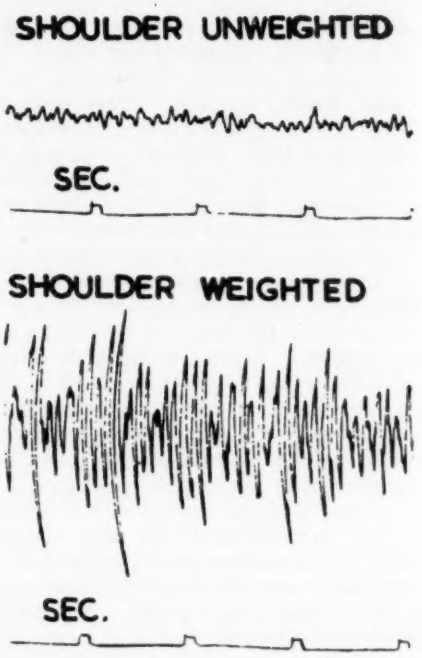


FIG. 3.—Record illustrating the effect of adding 4·3 kg. weight to upper arm during abduction.

As with the data discussed above we found, after having recorded these facts, that similar observations had been reported many years ago (Griffiths, 1888; Herringham, 1890). Intense voluntary effort may, however, make the waves increase in frequency. Thus when the extensors of the wrist are thrown into play with maximum force the waves recorded from the dorsiflexed hand were consistently found to increase in rate by a few cycles per second.

Characteristics of Physiological Tremor in Normal Children.—Six normal children, aged from 18 months to 9 years, were investigated. It immediately became apparent that the tremor, in all except the oldest, was slower than in the adults (Fig. 4). Slow rates of tremor were found both during movements and when the limbs were merely supporting their own weight. Slow tremor was found at the wrist, elbow, shoulder, ankle, and knee. At the hip the frequency was somewhat higher (Table II). When the limb was called upon to support an additional weight, except in one instance (F. J. W.), no consistent alteration in the frequency of the oscillations was observed, although in some of the records the disturbances were rather variable in frequency and small changes of a statistical nature would not be appreciated merely by examining the records visually. Young children are often notoriously clumsy in performing fine movements (cf. Montessori methods), and this slow frequency tremor must surely contribute

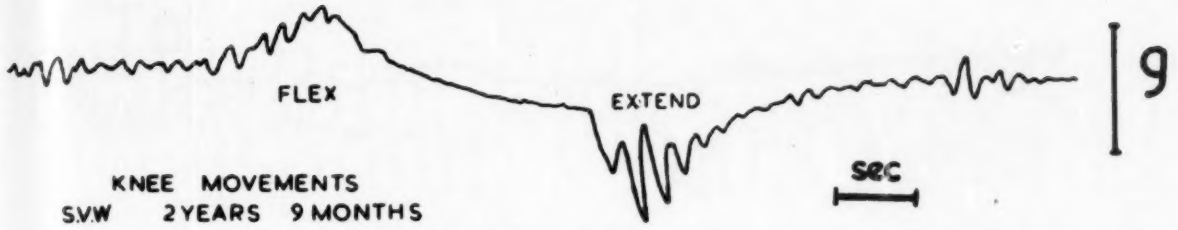


FIG. 4.—Physiological tremor during knee movements in a child.

TABLE II
FREQUENCY OF PHYSIOLOGICAL TREMOR IN CHILDREN

Child	Age (years)	Wrist	Elbow	Shoulder	Ankle	Knee	Hip
P.M.	1½	—	—	—	—	5	—
S.V.W.	2½	3-5	—	4-5 (4-5)	3½	3	8
J.P.W.	5	4½-5½ (3)*	4 (4)	4-5 (3-6)	5 (4)	4 (3-4½)	2 and 9 (two rhythms)
F.J.W.	5	6	3½ (7)	3½ (5)	5 (3½)	3½-4 (4)	1½ and 8½ (two rhythms)
M.M.	7½	5-7½ (4)	—	4 (5)	—	—	—
A.S.	9½	6-10	4-11 (8)	5-7 (5)	—	—	—

*Figures in brackets refer to tremor frequency with extra weight applied.

to this ineptitude. No previous investigations of physiological tremor in children have been traced.

Relationship to Electro-encephalogram.—Most of the observations recorded so far could be interpreted as the result of a central clocking mechanism facilitating the discharge of the motor neurons once every cycle (one-tenth of a second in the adult). There have been reported a number of observations that have been considered to favour the view that the excitability of the anterior horn cells fluctuates in time with the electro-encephalogram. That the tremor is slower in children might be regarded as in favour of this view for the waves of their electro-encephalogram also are of lower frequency. This hypothesis was tested in two ways.

Measurements were made of the moment at which a voluntary act was performed whilst the electro-encephalogram was recorded. Two subjects with a prominent alpha rhythm were chosen. It was found that the movements occurred at all phases of the alpha waves. Two experiments of this type are insufficient evidence on which to reject the hypothesis but an extended series of observations made elsewhere have yielded similar results (Crossland, personal communication).

The second approach was to show that muscular action tended to occur in jerks every 1/10 sec. after exclusion of the forebrain. Observations were made on two patients with complete division of the spinal cord. The accelerometer was attached to the foot and a flexor withdrawal reflex was elicited by stimulation of the sole of the foot with a pin, or by means of an electric current. The recordings that were obtained clearly showed the existence of a 10 c./sec. rhythm (Fig. 5).

Possible Synchronization of Motor Neurons.—A second hypothesis is that the rhythmicity is the result of synchronous discharge of different motor neurons. This problem is not readily solved by electrical recording from the interior of the muscle because it is so often uncertain, on recording synchronous discharges from different regions, whether the electrodes are recording from the same or from different motor units. Certain lines of evidence suggest that synchronization is not important for normal tremor:—

(1) Electromyography using surface leads gives no evidence of synchronization. Simultaneous mechanical and electrical recordings show the 10 c./sec. rhythm in the former but not in the latter (Fig. 6).

(2) The observations that have been made may be contrasted with conditions in which synchronization is established. Two forms of synchrony

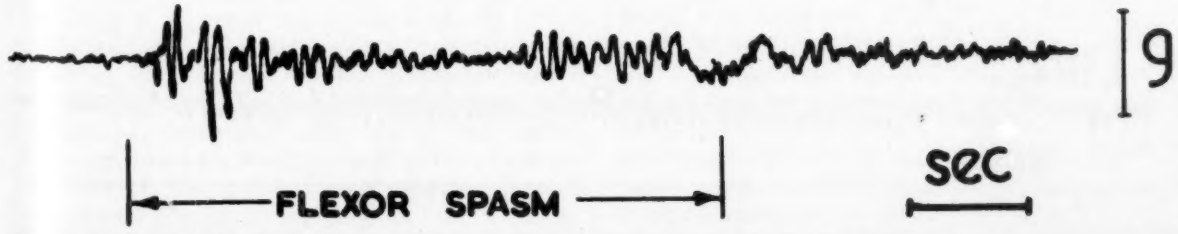


FIG. 5.—Tremor waves from foot during flexor spasm in an adult with complete transection of the spinal cord due to transverse myelitis.

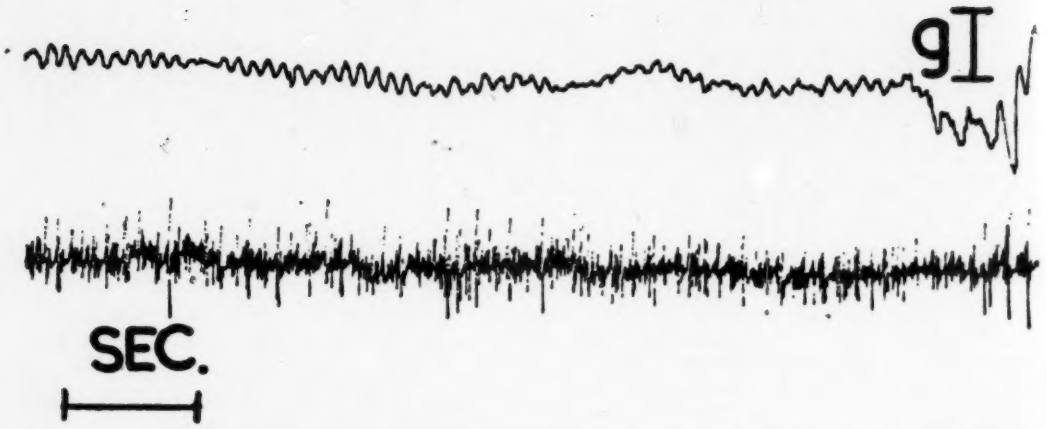


FIG. 6.—Simultaneous records of acceleration at wrist (upper trace) and electrical activity of wrist extensors recorded with surface leads (lower trace), show no evidence of synchronization in the electromyogram.

are known to occur in motor nerves: (*a*) A discharge of many elements at the same moment. This is found in clonus (Fig. 7). (*b*) A discharge of elements at different moments but with similar periods of activity and of quiescence, so that they fire in turn at different phases of the rhythmic movements. This type of synchrony is presumed to occur in Parkinsonism. In records of the acceleration of limbs with Parkinsonian tremor a 5 c./sec. and a 10 c./sec. tremor have sometimes been superimposed. This finding has been recorded by others also (Horsley, 1885; Wolfenden and Williams, 1888; Herringham, 1890).

The arguments against synchronization would gain force if it could be shown that the contraction of a single motor unit caused effects of an amplitude comparable to those of the tremor. It seemed logical therefore to study fasciculation. Accordingly, a series of five subjects was investigated who had, at some time in the past, suffered from poliomyelitis. Fasciculation is common long after an acute attack of this disease. We were struck by the observation that some unexpected movements were experienced by all but one of these patients. One electronic technician with wasting of the left forearm noticed that when he soldered with his right hand his left thumb " waltzed ". A general practitioner with wasting of the left deltoid noted that often when using his right hand to place his stethoscope on the chest of a patient his left deltoid contracted in a series of jerks. During the course of an investigation, one of the subjects (Miss M, aged 20) began to notice slight involuntary movements of the ankle. Electromyographic recording over the lower end of the calf revealed discharges of simple form (Fig. 8). When allowance is made for the undulations of the baseline the discharges are clearly of the " all or none " pattern. The discharge was followed over a period of 400 seconds. Although the frequency of the impulses varied their size was uniform. There was thus nothing to indicate that the discharge was due to a synchronization of motor units. This evidence, that the discharge of a single motor nerve fibre may give rise to small but detectable mechanical

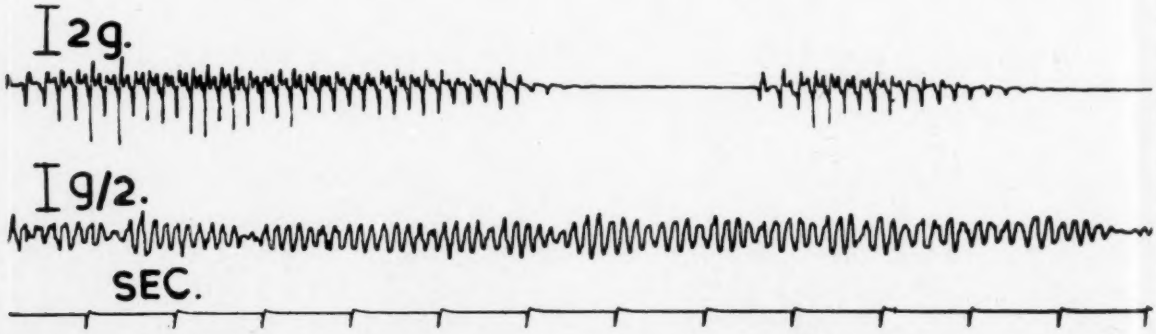


FIG. 7.—Record of rate of change of acceleration during two bursts of clonus from hemiplegic calf (upper trace) and during voluntary movement of normal calf (lower trace).

FIG. 8.—Single unit discharges recorded with surface leads during fasciculation in an adult with old poliomyelitis.

effects, loses some strength for it is possible that the units that survive in poliomyelitis are larger than normal. On the other hand, the effects of this unit were clearly greater than many of the waves of a physiological tremor.

If it is true that the discharge of a single motor nerve fibre could account for physiological tremor, it might be expected that the disturbances would be found as readily when few fibres were active as when many were coming into play. To obtain additional information on this point electromyography was performed using surface leads at a number of points on the musculature involved in the movements. To emphasize the discontinuities of the movement records were simultaneously made of the velocity of the acceleration. It was found that strikingly abrupt alterations were recorded from the mechanical transducer during the beginning of the movement, but these largely ceased during sustained contraction when many units had been recruited. On relaxation even more striking effects were seen at a time at which many units had dropped out of action. It sometimes happened that the most striking mechanical events occurred just after the electromyographic tracing had become quiescent. These findings are compatible with the production of the discontinuities by a single unit, or at most by a few units.

The Muscle as a Low Pass Filter.—During a steady voluntary contraction motor units start discharging at about 7 c./sec. (Adrian and Bronk, 1929) and thereafter increase up to about 50 c./sec. We wondered whether the relative constancy of the frequency of the tremor waves was due to the action of the muscle. If tetanic fusion of twitches began at about 10 c./sec. the nervous discharges would become progressively less well converted into mechanical changes at the higher frequencies. Measurements were therefore made of the excursions of various parts of the body when rhythmic electrical stimuli were applied to muscles.

Brief, exponentially decaying shocks were delivered to a number of skeletal muscles, the stimuli being applied to the motor nerve, or over the motor point. The movements were recorded by strapping the accelerometer over the belly of the muscle, or by registering the acceleration of the whole limb. A typical set of records is shown in Fig. 9. Very often there was a tendency for a resonance to occur at about 5 c./sec. Whilst this appeared to be mechanical, reflex effects were not definitely excluded. On raising the frequency to 10 c./sec., or a little beyond, there was a great decrease in the mechanical result. Various muscles behaved rather similarly (biceps, extensors of wrist, flexors of wrist, gastrocnemius, and the various components of quadriceps).

If the rhythmicity observed in mechanical records was due to the influence just mentioned it should be possible to modify the amplitude of the tremor by altering the behaviour of the muscle itself. Thus, if the muscle processes were slowed so as more readily to form a tetanus, the size of the waves should be reduced. We therefore arranged to cool the forearm in a bath of crushed ice and investigated the responses whilst the wrist was held steady and when it was flexed and extended. The most striking feature of the records was a reduction in the amplitude of the tremor waves. This was seen in each of the six experiments. Moreover, there appeared also to be a reduction in frequency.

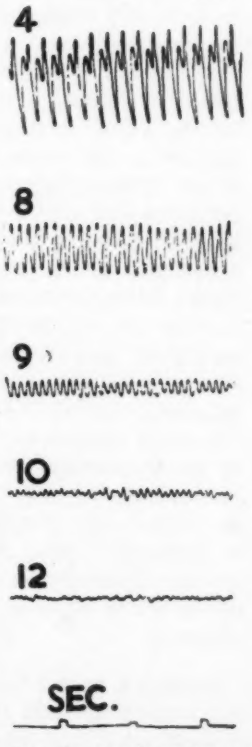


FIG. 9.—Accelerometer recording from wrist flexors during stimulation of motor point at the frequencies indicated by the figures.

Discussion

The Limb as a Pendulum.—Mechanical factors must be considered when discussing any form of tremor. Is it possible that the 10 c./sec. waves were due to the limb acting as a pendulum? Pendular knee jerks may illustrate this possibility. The limb is set moving by a brief contraction of the quadriceps, but the oscillations that follow are determined by the moment of inertia of the leg and foot. In such pendular action it is necessary to consider also any elastic elements operating across the swinging joint. The elasticity of muscles must be an important factor in determining the natural period of the arm when it is abducted. If the muscle is contracting powerfully the natural period will tend to be high; if it is relatively lax the natural period will be low. In moving a limb or part of a limb it is necessary to consider an instability that arises in terms not of neural or mechanical factors but in terms of the interaction of such effects.

In considering neural and mechanical interactions we may think of an oscillator (neural element) exciting a tuned circuit (mechanical element). Greatest effects will be expected when the oscillator operates at the same frequency as the tuned circuit. In a rapidly executed movement the tension of the muscles will be varying through a wide range continuously throughout the course of the movement. With such a brief contraction, therefore, the tuning of the limb segment will be constantly changing and no particular frequency will be emphasized. If the ripples of physiological tremor were due to a pendular-like action they should vary in duration according to the phase of the motion. No such systematic fluctuation has been observed. With longer lasting movements the tension exerted by the muscle can be fairly uniform over a significant period of time (isotonic contraction) and during this period the natural period of the segment will be relatively constant. Ripples of moderately constant repetition frequency may, therefore, be expected in the mechanical record. One conclusion would immediately follow: the more slowly a given movement was completed the lower the frequency of the irregularities. As the duration of a movement can be adjusted over a wide range there should be no difficulty in detecting this effect. It was not observed.

Feedback in the Stretch Reflex.—The possibility was considered that the tremor might be the result of feedback round the stretch reflex, but the evidence did nothing to support this possibility. The relevant facts may be summarized:—

(1) The similarity in the frequency of the tremor recorded from regions having short pathways to the cord with that of the waves from the distal parts of the extremities.

(2) The increase in the frequency of the waves during growth whilst the H reflex latency doubles between age of 6 and adult life (Wagman, 1954).

(3) The evidence that physiological tremor may be found after division of the posterior roots (Altenburger in Bumke and Foerster, 1937, Fig. 162, p. 957, Vol. III; Lashley, 1917).

(We hoped to obtain useful information by studying tabes but our two sets of observations were confusing; in one patient a 5 c./sec. tremor was prominent, in another no definite tremor was recorded. This problem needs further investigation.)

Relationship to the Alpha Rhythm.—The occurrence of the 10 c./sec. tremor in muscles innervated by a part of the spinal cord which was completely isolated from the forebrain excluded any possibility of its being determined by the alpha rhythm.

Possible Mechanism Underlying Physiological Tremor.—The similarity of the frequency of physiological tremor at a number of sites indicates, it is suggested, not the existence of a central pacemaker, but similarities in the behaviour of different motor neurons of the striated musculature with which they are connected. It is necessary to reconcile two findings: (1) the tremor frequency does not vary either with the velocity of the movement or with the load; (2) the discharge frequency of individual motor units is known to increase with increased effort (Adrian and Bronk, 1929).

We believe that two facts are relevant to an explanation of this apparent paradox: (1) Muscle stimulated more frequently than 15 times a second does not impart corresponding mechanical shocks of significant amplitude to the limb. (2) Motor neurons when first recruited in a steady voluntary effort discharge at about 7 c./sec.

Adrian and Bronk (1929) believed that during steady effort the motor neurons discharged asynchronously. Direct proof of this is difficult to obtain but no reason has been found for disagreement with their conclusion. Physiological tremor appears, therefore, to be an inevitable result of there being a finite number of motor nerve fibres. A rate of discharge below about 15 c./sec. in the motor fibres is converted to mechanical ripples by the muscles, but higher rates of neural discharges are blocked or filtered by the physical constitution of the muscle. We failed to detect differences in the behaviour of different muscles when studying the limbs, although in animals having red and white muscles differences are seen in response to repetitive stimuli. It is known, however, that the human extra-ocular muscles have high tetanic fusion

frequencies. The rate of discharge of the corresponding motor neurons also is known to be higher than in the case of the limbs. These considerations seem to explain the exceedingly rapid tremor of the eyeball (Table I).

The regular tremor would not be seen if, when first recruited, the motor units started to operate at higher frequencies, but the result would be jerky for the full tetanic tension would be realized abruptly. On the other hand, too low a rate of initial discharge would result in an accentuation of the tremor. To obtain smooth control of movement it is clear that the behaviour of motor neurons must be rather closely matched to the properties of the muscle which they control. It is not known whether special mechanisms exist to secure this correlation throughout life.

Summary

Physiological tremor has been studied by the use of a valve sensitive to acceleration.

The tremor has been found to be similar in frequency (about 10 c./sec.) at a number of different sites.

Electromyography revealed no definite evidence of a synchronization of motor units at this frequency.

The relative constancy of the frequency appears to be due to a fusion of twitches at higher rates.

Lower rates of tremor are found in young children.

References

Adrian, E. D., and Bronk, D. W. (1929). *J. Physiol.* (Lond.), **67**, 119.
Bumke, O., and Foerster, O. (1937). *Handbuch der Neurologie*, Vol. 3, Fig. 162, p. 957. Springer, Berlin.
Ditchburn, R. W., and Ginsborg, B. L. (1953). *J. Physiol.* (*Lond.*), **119**, 1.
Eliasson, S., and Gisselsson, L. (1955). *Electroenceph. clin. Neurophysiol.*, **7**, 399.
Griffiths, W. (1888). *J. Physiol.* (*Lond.*), **9**, 39.
Harris, D. F. (1894). *Ibid.*, **17**, 315.
Haycraft, J. B. (1890). *Ibid.*, **11**, 352.
Herringham, W. P. (1890). *Ibid.*, **11**, 478.
Hill, A. V. (1949). *Proc. roy. Soc. B.*, **136**, 420.
Horsley, V. (1885). *Brit. med. J.*, **1**, 111.
——, and Schäfer, E. A. (1886). *J. Physiol.* (*Lond.*), **7**, 96.
Lashley, K. S. (1917). *Amer. J. Physiol.*, **43**, 169.
Schäfer, E. A. (1886). *J. Physiol.* (*Lond.*), **7**, 111.
Wagman, I. H. (1954). *J. Neurolphysiol.*, **17**, 66.
Wolfenden, R. N., and Williams, D. (1888). *Brit. med. J.*, **1**, 1049.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 268.

SUBACUTE MYOCLONIC SPINAL NEURONITIS

BY

A. M. G. CAMPBELL and HUGH GARLAND

From the Departments of Neurology, Bristol Royal Hospital, and the General Infirmary at Leeds

The object of this paper is to record three examples of a neurological disorder which we think has not been previously observed. The three patients, seen in 1948 and 1954, seem to have been clinically identical and in the two who died there are striking similarities in the histological changes in the spinal cord. The most striking clinical feature in all three was myoclonus, largely limited to the legs. Histological studies suggest that the syndrome resulted from attack by a virus and in the two fatal examples previous *x*-irradiation may have been an aetiological factor.

Case Reports

Case 1.—A man, aged 30, a parcels vanman, was admitted to Southmead Hospital, Bristol, on August 24, 1954, complaining of general malaise with myoclonic contractions and stiffness of the legs.

He was found to be a diabetic at the age of 25 and since then had been taking 30 to 40 units of zinc protamine insulin (Z.P.I.) daily. There was nothing relevant in his family history. In December, 1953, he was seen by an orthopaedic surgeon because of low back pain. He was treated with a plaster jacket without benefit and in April, 1954, was considered to be suffering from ankylosing spondylitis, although at that time the blood sedimentation rate was normal and radiological changes in the spine were indefinite; at the same time, chest expansion was limited and back movements were stiff. He was referred to a radiotherapist and given between 900r and 1,100r in 31 days to the whole of the spine, the higher dose being given in the mid-dorsal region. Treatment was completed on July 1, 1954. The skin received 1,800r and the upper limit of treatment was about the second cervical vertebra. When last seen by the radiotherapist on August 18, 1954, he still had lumbar pain though it was now radiating down the legs.

On admission to hospital on August 24, 1954, there was constant though very variable contraction of all the muscles of the abdominal wall and the legs. The contractions occurred in attacks which were at the rate of about 20 a minute and each muscle spasm was associated with severe pain and excessive sweating. The temperature had risen to 102° F. The diabetes had become difficult to control and the dose of Z.P.I. had to be increased to 50 to 60 units daily. During the next few days the muscular contractions spread into the chest muscles and the sternomastoids and the temperature rose to 104° F. On August 31 the intercostal muscles were so involved that there was difficulty with respiration; when the respiratory rate had risen to 48 the patient became disorientated and confused. Intramuscular sedatives had little effect. It was then noticed that the slightest external stimulus would precipitate muscular contractions and for this reason detailed examination of the nervous system was limited, though no other abnormality was detected. By this time morphia was found to be one of the most satisfactory drugs in controlling the muscle spasms. It was at this stage that he was first seen by one of us (A.M.G.C.), but on that date the respiratory rate continued to rise, he became delirious, and died before artificial respiration had been attempted.

Histological Examination.—This was performed by Dr. R. M. Norman, at the Frenchay Hospital, Bristol, and the following is his report:—

The brain and spinal cord were normal to the naked eye.

Blocks of tissue were taken from representative areas of the cerebral cortex, basal ganglia, cerebellum, pons, and medulla. The spinal cord was sampled from cervical, thoracic, and lumbar segments. Celloidin sections were stained for nerve cell bodies by carbol azure and for myelin by Heidenhain's method. The following methods were used with frozen sections; Bielschowsky's stain for axis cylinders, Scharlach R. for lipid, Holzer's method for fibrillary astrocytes, and Anderson's modification of the Kultschutzy-Pal stain for myelin. Paraffin sections were stained by haematoxylin and eosin.

Spinal Cord.—Perivenous cuffing by lymphocytes was seen at all levels (Fig. 1), its intensity varying from section to section but the inflammatory cells rarely exceeded a depth of two or three rows. Cuffing was most conspicuous in the zone of white matter adjacent to the cornua, the vessels often being dilated but not showing extravasation of red cells or oedema fluid. The leptomeninges of the anterior fissure contained a few lymphocytes.

Microglial cells in the white matter generally exhibited a faint staining of their processes in the carbol azure (Nissl) preparations, but no hypertrophic forms were present. Localized aggregations of microgliocytes were seen either in relation to small blood vessels or as isolated glial stars and seldom exceeded six per section (Fig. 3). In the anterior horns microglial nuclei were

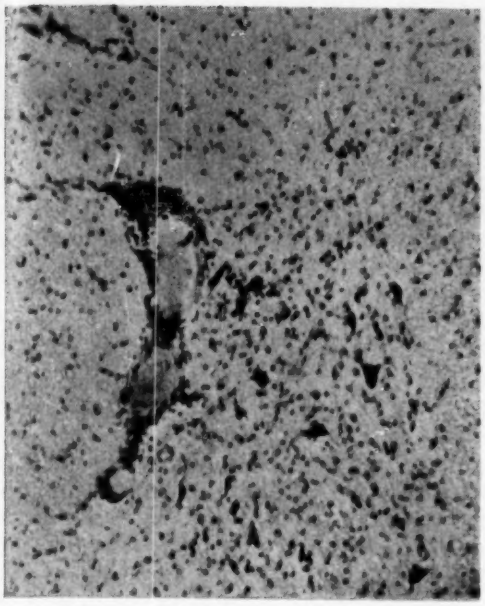


FIG. 1

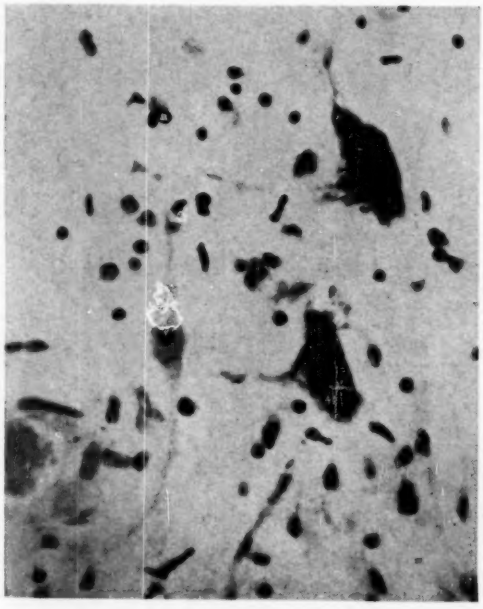


FIG. 2

FIG. 1.—Case 1: Spinal cord, a mid-thoracic segment. Lymphocytic cuffing of vessels. Carbol azure stain, low power.

FIG. 2.—Case 1: Shrunken, chromatolytic nerve cell in the anterior horn of a cervical segment. Carbol azure stain, high power.

FIG. 3.—Case 1: A microglial nodule in the white matter of the spinal cord. Carbol azure stain, high power.

FIG. 4.—Case 1: Cervical spinal cord. A figure of neuronophagia in the anterior horn.

FIG. 5.—Case 1: A microglial star in the lateral cuneate nucleus.

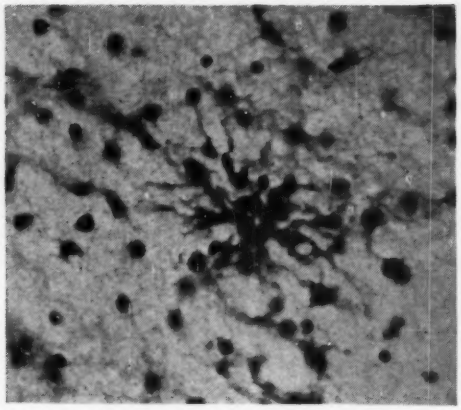


FIG. 3

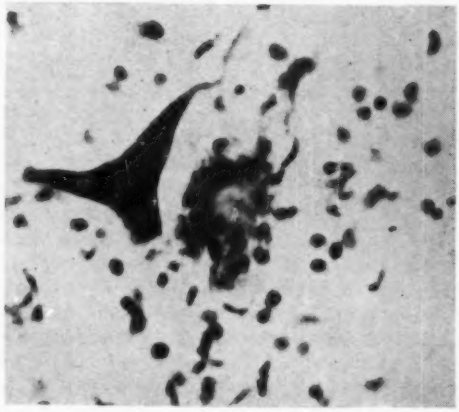


FIG. 4

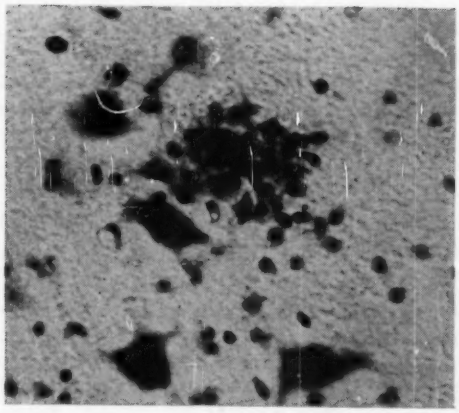


FIG. 5

sometimes grouped around poorly staining nerve cells and a few denser nodular formations resembling figures of neuronophagia were occasionally found (Fig. 4). Especially in the cervical cord a more diffuse proliferation of microglia could sometimes be demonstrated and this gave a patchy, increased cellularity to the grey matter.

The majority of the nerve cells had normal nuclei and Nissl substance, though the cytoplasm of many stained darkly with carbol azure. Some shrunken, deeply stained anterior horn cells with wavy processes were present at all levels of the cord and a few faintly staining small neurons were also seen. In the latter cells the Nissl bodies had disappeared, the cytoplasm staining a uniform pale blue colour with carbol azure or pink with eosin (Fig. 2). The nuclei usually stained poorly and in some instances showed merely as a few fine chromatin particles. Only a few of these degenerate cells showed satellitosis by microglial cells.

Brain.—A small number of microglial nodules were seen in the medulla (Fig. 5), and also in the central white matter of the cerebellum. There was a sparse and patchy lymphocytic infiltration of the cerebellar leptomeninges. Cuffing of the vessels was only seen in one situation above the level of the spinal cord, namely, in the internal capsule. Some of the nerve cells in the substantia nigra had shrunk markedly but no free pigment or glial activity was present. Here and there, in the centrum semiovale and cores of gyri, perivascular spaces had become widely dilated. The conspicuous lacunae so formed were filled with a delicate glio-mesodermal meshwork which contained small groups of compound granular corpuscles and showed a mild gliosis at their margins.

Elsewhere in the brain no significant pathological changes were found in the numerous areas examined.

In this case the lymphocytic cuffing and microglial nodules, which are features common to many types of virus infections of the nervous system, were almost exclusively found in the spinal cord. The absence of polymorphonuclear infiltration and the inconspicuous damage to the anterior horn cells distinguishes the condition from poliomyelitis. It is more difficult to rule out encephalitis lethargica as the pathogenetic agent, though there were no inflammatory lesions in the sites of predilection of this disease, namely the substantia nigra, periaqueductal grey matter, hypothalamus, or the region of the third ventricle. It is, however, well known that the spinal cord may rarely be substantially implicated in this condition. There are also great variations in the severity of the pathological process in encephalitis lethargica, and in those dying about a week after the onset of the illness there has been a discrepancy similar to that seen in the present case between the severity of the neurological illness and the paucity of the demonstrable neuronal damage.

Two other pathological findings in this case require comment. The abnormally dense gliosis found in the white matter of the spinal cord clearly antedated the terminal illness and is probably to be regarded as a sequel to the radiotherapy of the spine. Damage to the astrocytes is a prominent feature of the lesions produced by irradiation of experimental animals and it is reasonable to suppose that milder dosage could induce proliferative changes. The dilatation and fibrosis of the perivascular spaces seen here and there in the white matter of the hemispheres are also evidently unrelated to the encephalitic process.

The most striking features of this case were the sudden onset of a febrile illness associated with widespread mycolonus, severe pain, and drenching sweats. At all stages the legs were most severely involved, though there was terminal spread to the respiratory and sternomastoid muscles. The nature of the histological changes would make it fairly certain that the main aetiological factor was a virus infection.

Case 2.—A man, aged 35, a railway shunter, was admitted to Ham Green Hospital, near Bristol, on July 4, 1954. He was very ill with profuse sweating and involuntary spasms of the abdominal muscles occurring every few minutes.

The only feature of the previous history that might be relevant was that he suffered from canicola fever with lymphocytic meningitis (serological proof) in 1949; this was followed by no sequelae. On July 3, 1954, he complained of a sore throat and the following day had violent involuntary spasms of the abdominal muscles, particularly the recti, which the patient likened to severe hiccoughs. Apart from these spasms, which occurred with great regularity every few minutes, neurological examination appeared to be negative. The spasms were painful though the pain disappeared as the muscles relaxed; they occurred both day and night and prevented sleep. They continued during the next few days and disappeared towards the evening of July 6. During this period the temperature was 101 to 103° F., the pulse rate 105, and the respiration rate 24. The cerebrospinal fluid on July 4 was normal in all respects, The blood picture showed a leucocytosis of 16,900 (polymorph cells 87%) on July 5, though the count had fallen to normal on July 7. Blood culture was sterile and paired samples of blood for virus investigations produced negative results. The patient made a rapid recovery and apart from slight giddiness on getting up on July 14 he had no further symptoms. He was last seen on April 25, 1955, when he was normal and working.

This patient resembles Case 1 in some respects. The myoclonic jerks were limited to the abdominal muscles, each phase of myoclonus was of shorter duration, and the intervals between these phases much longer; otherwise there was a strong similarity in the appearance of the muscle spasms. Again the myoclonus was associated with severe sweating and with pyrexia. This patient had not been subjected

to radiotherapy but had had a previous meningeal illness which may or may not be relevant.

Case 3.—A man, aged 32, was admitted to the General Infirmary at Leeds on December 15, 1947, with a three-month history of swelling of the face and neck resulting from mediastinal compression. Radiographs of the chest showed several large masses on either side of the mediastinum and independent of the aorta; it was thought that the pathology was either Hodgkin's disease or lymphosarcoma. The Wassermann reaction was negative. The patient was given a course of deep *x*-ray therapy to the dorsal region on eight days between January 2 and January 16, 1948; the rays were applied over the lumbar and thoracic regions only. The symptoms improved markedly and he was discharged on January 16; subsequently the radiological shadows disappeared entirely.

On April 18, 1948, he began to notice stiffness of the legs which rapidly became worse so that he was unable to walk on April 22, and by this time he had noticed frequent involuntary twitching of the leg muscles. He was readmitted to the General Infirmary at Leeds on April 28, and by this time had extremely severe and painful spasms of the legs, accompanied by drenching sweats. Any type of stimulus to the legs evoked a painful spasm, so that detailed examination was impossible. The temperature had already risen to 105° F., though this was lowered by tepid sponging. The twitching was so frequent and so distressing that he was given a spinal anaesthetic under pentothal anaesthesia; cerebrospinal fluid removed at that time was normal in all respects. The spinal anaesthetic gave complete relief from muscle spasms for about 24 hours, after which they recurred but were again relieved by a spinal anaesthetic. A number of drugs were tried in an effort to control the spasms, including morphia, pentothal, pethidine, and avertin, but relief was negligible and finally curare was given; in the first instance 60 mg. in an aqueous solution was given over a period of four hours. This produced relief from the spasm and later 30 mg. was given three hourly, with considerable relief. By May 14 a reasonable control had been established by the use of 50 mg. curare in oil together with 10 mg. in an aqueous solution, each given at three-hourly intervals. About this time a little twitching had appeared in the sternomastoid muscles as well as in the abdominal and spinal muscles and it became necessary to increase the dose of curare. At this stage it became essential to use an artificial respirator, and the patient died on May 24, 1948. Over the period of 16 days this patient was given 3,065 mg. of curare (2,625 in oil and 440 in aqueous solution). Towards the end of the illness, although physical examination remained impossible, it was thought that he had developed a lower motor neuron type of weakness in the legs.

Histological Examination.—This was done by Dr. J. G. Greenfield at the National Hospital, Queen Square, London. He reports as follows:—

No macroscopic abnormality was seen in the brain or spinal cord.

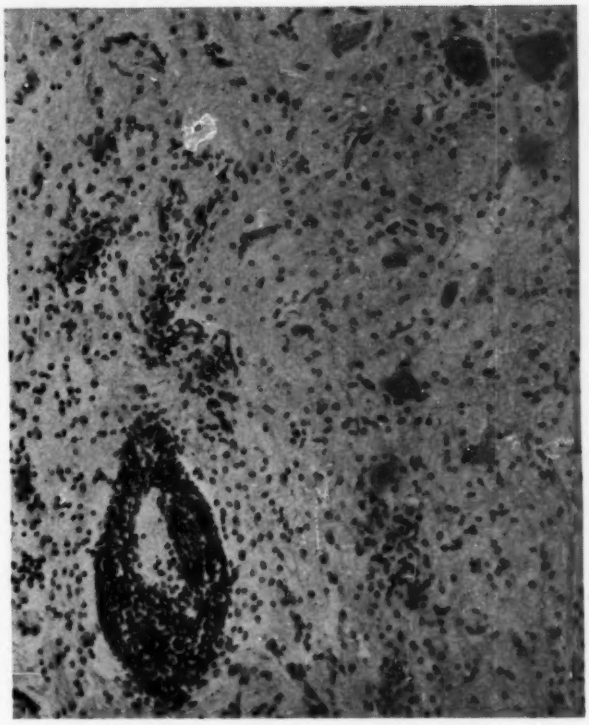


FIG. 6.—Case 3: L.4. There is lymphocytic cuffing of a vessel and several anterior horn cells are undergoing neuronophagia. (Haematoxylin and eosin.)

Sections were made of motor cortex and basal ganglia in the coronal plane through the posterior half of the putamen and globus pallidus and thalamus, including the convoluted area of the hippocampus. These and sections through the mid-brain and cerebellum showed no abnormality.

In the medulla the only abnormality was in an area in the descending trigeminal nucleus where there were two vessels cuffed with lymphocytes and small foci of microglial overgrowth rather larger and more diffuse than glial stars. The cervical cord was normal.

In the third, fourth, and fifth thoracic segments there were several nerve cells in both ventral and dorsal horns which showed degeneration with rings of microglial cells round them, as well as cuffed vessels in the grey matter. Lesions of this kind of slight but variable intensity were seen in the lower thoracic segments, but in the lumbar and sacral segments reached their greatest intensity (Fig. 6). They affected the dorsal horns down to their cap of grey matter, which at some levels was very heavily infiltrated in a focal manner. There were also heavily infiltrated vessels running out through the white columns, but these were otherwise quite normal. The nerve cells, which were ringed by phagocytes, had a darkly staining nucleus and usually had lost their more central Nissl granules (Fig. 7), but many retained a layer of these under the surface of the cell. No inclusion bodies were seen in them with ordinary staining methods. Certainly a larger proportion of neurons in the dorsal than in the ventral horns were degenerated and Clarke's column did

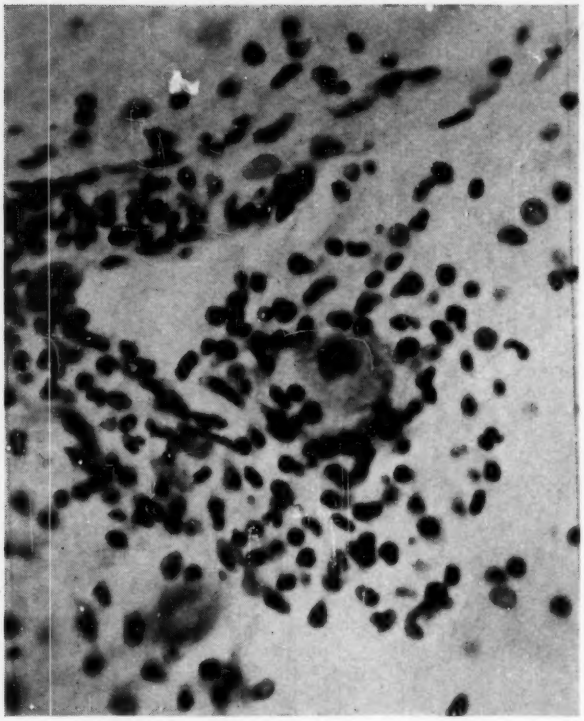


FIG. 7.—Case 3: L.3. High power view of a nerve cell in the anterior horn surrounded by inflammatory cells and showing diffuse chromatolysis and early nuclear damage. (Haematoxylin and eosin.)

not escape. Some cells showed rings of cells round them but little change, others were degenerated but had no excess of cells in their vicinity. Perivascular infiltration was here intense. No vascular changes were seen except in a few intramedullary arterioles at L.5 and S.1 where the media was thickened and rather hyaline.

There was no doubt that some clumps of microglial cells overlay the remains of nerve cells both in the ventral and dorsal horns. The appearance in that respect (in the ventral horns) resembled poliomyelitis.

The appearances seemed to be altogether in favour of the diagnosis of " subacute encephalomyelitis ", *i.e.*, an infection, presumably of virus nature, involving the grey matter both ventral, dorsal, and central of the cord and medulla. The virus of poliomyelitis did not seem to be implicated as the dorsal horns were so much more affected and clinically there appeared to have been little resemblance.

There seems little doubt that the clinical syndrome in this patient was the same as that in the two previous examples and equally little doubt about the histological identity of Cases 1 and 3. The presumed malignant masses seen radiologically in December, 1947, had left no trace at the necropsy, though it would seem a reasonable assumption that, whatever their precise nature, they would recur. It is doubtful whether anything more could have been done for this patient at the time, though it seems highly probable that with methods of artificial respiration available in 1956 his life could have been saved as far as the neurological syndrome was concerned. The increased neuronal damage seen in Case 3 can be explained on the longer duration of the illness, six weeks compared with one week.

Discussion

The clinical similarity of these three cases is undoubted; all showed involuntary myoclonic movements beginning in the legs and trunk, and in all there was a high fever with severe sweating. The pathological picture confirmed that in two the damage was most extensive in, indeed largely limited to, the spinal cord. The myoclonic movements appear therefore to have originated in the spinal cord itself and the pathogenic agent concerned appears to have produced an excitatory reaction rather than a paralytic one. Recent discussion on myoclonus and its origin has shown that no pathology is peculiar to the condition, and it can be associated with cortical, cerebellar, and brain-stem lesions; in our cases the myoclonus was almost certainly determined by the spinal cord disease.

Friedreich (1881) described paramyoclonus multiplex, which consisted of myoclonic contractions of the trunk and extremities rarely involving the face. The contractions were short and lightning-like but involved a large number of muscles without moving the limb, the twitching being separated by various time intervals. Bradshaw (1954) defined myoclonus as " a disturbance of neuronal activity characterized by very sudden, involuntary jerks which are arhythmic and asynergic involving portions of muscles, whole muscles or muscle groups ". He suggested that during relaxation an excitatory status is set up by neurons concerned with muscle strength and that this appears to be at spinal level in certain cases since there is no involvement of the cranial nerves and no cortical " march ". He suggested that, as in our cases, physiological afferent impulses produce a sufficient stimulus to provoke involuntary jerks. He also suggested that intercalated neurons within the dorsal horn are primarily affected and that the anterior horn cells are only affected secondarily. It appears that the neuronal activity in our patients arose in this way from the spinal cord.

Van Bogaert, Radermecker, and Titeca (1950) have reviewed the causes of myoclonus and mention the infective-encephalitic group. They emphasize that myoclonus has been recorded particularly in subacute inclusion encephalitis in children and occasionally in encephalitis associated with specific fevers such as whooping cough. In particular

myoclonus was occasionally a characteristic of encephalitis lethargica. Von Economo (1931) in his monograph describes a hyperkinetic poliomyelitic form of encephalitis lethargica associated with extensive brain-stem damage, and discusses the very severe myoclonic contractions which occur in this type of the disease. Many of the victims began with rigidity of the legs followed by myoclonic jerks of leg and abdominal muscles and, as in our cases, the abdominal pain was so severe from contraction of the recti that some surgical abdominal catastrophe was considered in the differential diagnosis.

Sicard (1920) was one of the first to emphasize myoclonic encephalitis lethargica and Walshe (1920), quoting one of Sicard's cases, said that the myoclonus was followed by lower motor neuron peripheral paralysis of the arm after the contractions had ceased, probably indicating that the anterior horn cell was the common factor in both the myoclonic contractions and the subsequent paralysis.

That certain examples of encephalitis lethargica showed spinal cord damage there is no doubt, but whether it resembles in any way the damage shown in our patients is difficult to say. Many viruses can attack the nervous system and it is impossible to be certain without an epidemic that sporadic cases really fall into this group. Cases resembling encephalitis lethargica may still occur sporadically.

The other interesting point about two of these patients was their exposure to radiotherapy. It seems more than a coincidence that two out of three examples should have had radiotherapy to the spine less than six weeks before the onset of their neurological illness. The third patient had a neurological illness taking the form of meningitis, and possibly encephalitis, four years before. Perhaps the *x* rays and the canicola fever acted upon the nervous system in such a way as to predispose to later infection with a virus by lowering the resistance to that virus or by altering the immunity reaction of the nervous system. Clemente and Holst (1954) have shown that there is considerable disturbance of the blood-brain barrier after exposure to *x*-ray treatment and they showed by the passage of trypan blue dye that permeability of this barrier is greatly increased.

This hypothesis receives some support from several observations appearing in the literature, which have suggested a causal relationship between irradiation and subsequent infection. One of the first was made by Lyman, Kupalov, and Scholz (1933) who noted that three out of four irradiated dogs developed a distemper-like encephalitis. In two of these animals the inflammatory changes were widespread and not symptomatically related to areas of radiological exposure.

Pendergrass, Hodes, and Groff (1940) reported three human cases of purulent infection of the brain or its covering following large doses of *x* rays given for a carcinoma of the scalp, and in the discussion following this paper Dyke referred to several incidents of epidural abscess occurring weeks or months after irradiation for a tumour.

Schaltenbrand (1935) described an illness resembling encephalitis, later followed by epilepsy, in a child whose scalp had been exposed to radiotherapy.

These examples strongly support the theory that the resistance of the nervous system to either pyogenic or virus infection may become impaired as a result of previous irradiation. The wide acceptance of the statement that the central nervous system is relatively insensitive to *x* rays has encouraged excessive dosage and a disregard for its dangers in human patients. Pennybacker and Russell (1948) have already shown that massive focal necrosis and gliosis follow irradiation of the brain after a latent period of five to nine years. This latent period is difficult to explain but they suggest that the damage is probably secondary to fibrinoid necrosis, fibrosis, and vascular damage, and is a very slowly progressive process gradually producing the later clinical effects. They also suggest that vascular permeability may be a factor. The examples they dealt with were entirely brain lesions, but Stevenson and Eckhardt (1945) have described necrosis in the spinal cord and have emphasized the dangers that may occur with irradiation of the spine.

It does not seem to us likely that the generalized increase in neuroglia in the spinal cord in our first case was the consequence of irradiation, as might possibly be suggested. It is striking in our two cases exposed to irradiation that there was the same latent interval between the exposure and the development of symptoms. This would suggest that the *x* rays produced a slowly progressive damage lowering the resistance to an infective process some time after the cessation of exposure.

Summary

Three patients are described who appear to have been suffering from an identical syndrome; further weight is lent to its identity by the similarity of histological changes in two fatal examples.

The illness pursued a subacute and probably always reversible course characterized by violent myoclonus largely confined to the legs.

The histological changes are those of an inflammatory lesion confined to the grey matter of the cord, particularly in the dorsal and lumbar regions.

X-irradiation of the spine may have played an aetiological role.

We are grateful to Dr. James Macrae for referring Case 2 to one of us (A.M.G.C.) and to Professor T. F. Hewer and Dr. H. Urich for reference of post-mortem material in Case 1.

References

Bogaert, L. van, Radermecker, J., and Titeca, J. (1950). *Folia psychiat. (Amst.)*, **53**, 650.
Bradshaw, J. P. P. (1954). *Brain*, **77**, 138.
Clemente, C. D., and Holst, E. A. (1954). *A.M.A. Arch. Neurol. Psychiat.*, **7**, 166.
Economo, C. von (1931). *Encephalitis Lethargica*, trans. Newman, K. O. Oxford University Press, London.
Friedreich, N. (1881). *Virchows Arch. path. Anat.*, **86**, 421.
Lyman, R. S., Kupalov, P. S., and Scholz, W. (1933). *Arch. Neurol. Psychiat (Chicago)*, **29**, 56.
Pendergrass, E. P., Hodes, P. J., and Groff, R. A. (1940). *Amer. J. Roentgenl.*, **43**, 214.
Pennybacker, J., and Russell, D. S. (1948). *Journal of Neurology, Neurosurgery, and Psychiatry*, **11**, 183.
Schaltenbrand, G. (1935). *Nervenartz*, **8**, 62.
Sicard, J. A. (1920). *Bull. Soc. méd. Hp. Paris*, **44**, 294.
Stevenson, L. D., and Eckhardt, R. E. (1945). *Arch. Path. (Chicago)*, **39**, 109.
Walshe, F. M. R. (1920). *Brain*, **43**, 197.

THE AUGUST (1956) ISSUE

The August (1956) issue contains the following papers:—

Diffuse Degeneration of the Cerebral White Matter in Severe Dementia Following Head Injury. Sabina J. Strich.

Retinal Degeneration in Hereditary Ataxia. Å. Björk, U. Lindblom, and L. Wadensten.

Paroxysmal Dysphasia and the Problem of Cerebral Dominance. H. Hécaen and Malcolm Piercy.

The Prolonged and Distant Effects of Experimental Brain Injury on Cerebral Blood Vessels as Demonstrated by Radioactive Indicators. James B. Brierley.

Multilocular Encephalomalacia. W. Kramer.

The Pathological Effects of Cerebral Arteriography. T. Crawford.

Electrophoresis of Sera in Multiple Sclerosis and Other Neurological Diseases. Elizabeth M. Press.

Benign Congenital Myopathy with Myasthenic Features. John N. Walton, Norman Geschwind, and J. A. Simpson.

A Controlled Clinical Study of Chlorpromazine and Reserpine in Chronic Schizophrenia. Michael Shepherd and David C. Watt.

Book Reviews.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12*s.* 6*d.*

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 275.

ELECTRICAL SIGNS IN THE DIAGNOSIS OF CARPAL TUNNEL AND RELATED SYNDROMES*

BY

JOHN A. SIMPSON

From the Neurological Research Unit and the Department of Applied Electrophysiology, National Hospital, Queen Square, London

A common problem in clinical neurology is the differential diagnosis of the cause of tingling or numbness of fingers which may be associated with weakness of the small muscles of the hand. There is general recognition that the syndrome may result from compression of nerve roots or peripheral nerves supplying the hand, or of the blood vessels supplying the affected nerves, and that compression may occur at various sites in the spine (Brain, Northfield, and Wilkinson, 1952), thoracic outlet (Walshe, 1951), and more peripherally. The median nerve is commonly compressed in the carpal tunnel on the flexor aspect of the wrist (Kremer, Gilliatt, Golding, and Wilson, 1953) and the diagnosis is of considerable importance in view of the efficacy of decompression of the carpal tunnel (Brain, Wright, and Wilkinson, 1947).

Electromyographic diagnosis has hitherto depended on the demonstration of evidence of partial denervation confined to the muscles supplied by a particular motor nerve or one of its branches. This method has certain practical disadvantages. It may fail to demonstrate changes at an early stage which are diagnostic and it necessitates widespread exploration of the intrinsic muscles of the hand with a needle electrode.

Considering that the pathological basis of these syndromes is presumed to be a local ischaemic lesion of a peripheral nerve or one of its branches it seemed worth examining patients for phenomena known to be present in experimental ischaemia of short lengths of nerves. These are (1) diminished conduction velocity of the nerve impulse through the ischaemic segment, and (2) repetitive firing of motor nerve fibres after a single electric shock stimulus (Kugelberg and Cobb, 1951).

Material and Methods

Clinical colleagues were invited to refer for study patients in whom the diagnosis of carpal tunnel syndrome seemed probable. The survey was subsequently extended to include patients in whom the diagnosis was less certain and confirmatory evidence was required. Seventeen patients were examined, two of whom had ulnar nerve lesions, one at the elbow and one of the deep branch at the wrist. Ten normal subjects, five patients with motor neuron disease, and 10 patients with various muscular diseases were examined as controls.

Cathodal stimulation was applied at various points along the course of the nerve with a brief condenser discharge (time constant 20 μsec.) which was triggered by the time-scale of the recording oscillograph at a point indicated on it. The stimuli were applied through an isolating transformer to reduce artefacts. An Ediswan E.E.G. electrode was used for the cathode and a large plate electrode over the upper arm as anode. Threshold or supramaximal stimuli (judged from the amplitude of the muscle action-potential) were applied once per second.

Electromyographic recordings were made through a coaxial needle electrode inserted into the abductor pollicis brevis or opponens pollicis for median nerve, and abductor digiti minimi or first dorsal interosseus muscle for ulnar nerve conduction studies. A surface electrode placed between stimulating cathode and needle electrode was connected to the earth terminal of the amplifier to diminish stimulus artefact in the records. The action potentials were amplified by a differential amplifier with an adequate frequency response, and displayed on one beam of a double-beam cathode ray oscillograph. The other beam was fed with a time-scale giving intervals of 1 and 10 m.sec. derived from a crystal oscillator.

Ten sweeps of the oscillograph beam were superimposed in the photographic record. The time-interval between the recorded stimulus artefact and the initial deflection of the summated muscle action-potential identified at maximum gain was measured at each site of stimulation. The length of nerve from stimulating cathode in each situation to the recording needle-electrode was estimated by surface measurement. Symmetrical points of stimulation and recording were compared in both arms. In a few instances the median and ulnar nerves of the same limb were compared.

Results

The latency of the earliest action potential recorded in the opponens pollicis of normal subjects

*Based on a paper read before the Association of British Neurologists on November 11, 1955.

when stimulating the median nerve just above the proximal crease on the flexor surface of the wrist was usually 3 m.sec. and never more than 5 m.sec. The latency from stimulation of the same nerve in the antecubital fossa to the same recording point was 8-12 m.sec., the variation depending mainly on the length of the limb. The time required for conduction of the impulse between the two points of stimulation can be obtained by subtraction. In 11 of the 15 patients in whom the carpal tunnel syndrome was thought to be present the latency of response was significantly increased (up to 14 m.sec. at the wrist) on one or both sides (Table I). Typical samples of the type of record from which the measurements were made are shown in Fig. 1.

Calculation shows that the delay can be entirely accounted for by slowed conduction distal to the wrist stimulation-site, which might be due to physiological abnormality in the carpal tunnel or delay in neuromuscular transmission. Owing to physical limitations it is impossible to decide between these alternatives by stimulation distal to the carpal tunnel. A comparable experiment, however, was possible in a case of right ulnar nerve paresis due to chronic trauma at the elbow, which had a permanent flexion deformity and increased carrying angle following faulty reunion of a fracture (Fig. 2).

TABLE I

DISTANCE FROM CATHODE TO RECORDING ELECTRODE WITH LATENCY OF FIRST EVOKED ACTION POTENTIAL IN ABDUCTOR POLLICIS BREVIS OR OPPONENS POLLICIS IN CASES OF CARPAL TUNNEL SYNDROME

Case	Right Median				Left Median			
	Elbow		Wrist		Elbow		Wrist	
	cm.	m.sec.	cm.	m.sec.	cm.	m.sec.	cm.	m.sec.
Normal	—	8–12	—	3–5	—	—	—	—
1	28·5	17	6	*11*†	28·5	10·5	6	4
2	28	12	5	*8*	28	10	5	4
3	34	12·5	7	*6·5*	33	13	6·5	*7*
4	28·5	11	5·5	*6*	29·5	8·7	6·5	4
5	31	11	5	5·5	30·5	9·5	6·5	5
6*†	—	—	—	—	25	13	5	*8*
7	27	9	5	5	30	19	5	*14*
8	33	18·5	7·5	*8·5*	34·5	15	8	*10*
9	32	9	6	3·5	33·5	9	5·5	4·5
10	28	9	6	5	—	—	—	—
11*	32·5	15	7·5	*10·5*	32·5	18·5	5·5	*13*
12	37	13	8	7	34	10	6	4·5
13	28	12·5	6·5	7	27	7·5	6·5	3·5
14	28·5	9	6	4	29	9·5	6	4·5
15*	30	20	6	*14*	29	18	6	*13*

*Normal conduction velocity demonstrated in ulnar nerve.
†Significant peripheral delay shown by figures in italics.

The ulnar nerve could be stimulated at two points in the upper arm proximal to the lesion and at two points in the forearm distal to it and the latencies of response of the earliest unit recorded from abductor digiti minimi compared with those recorded in a similar way from the left arm (Fig. 3).

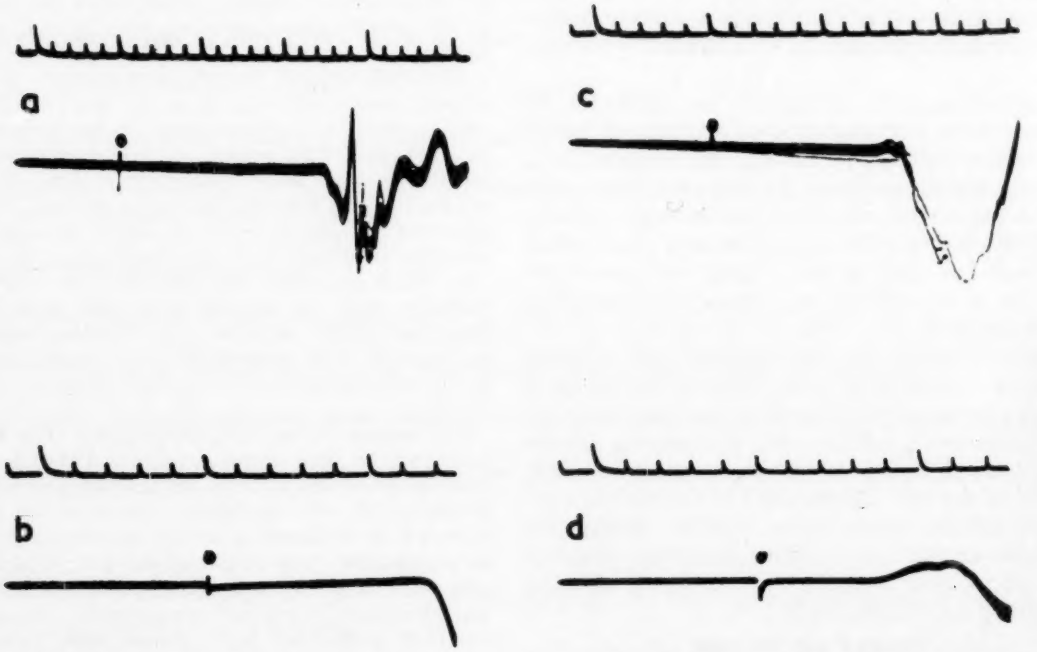


FIG. 1.—Case 13: Right carpal tunnel syndrome.

Ten superimposed action-potentials of right (*a*, *b*) and left (*c*, *d*) abductor pollicis brevis evoked by supramaximal stimulation of the appropriate median nerve at the elbow (*a* and *c*) and at the wrist (*b* and *d*). Stimulus marked by spot. Time marks 1 and 5 m.sec. in each record (scale varies).

	R. Median Nerve		L. Median Nerve	
	cm.	m.sec.	cm.	m.sec.
Elbow	28	12·5	27	7
Wrist	6·5	7	7·5	3·5

The latencies were virtually identical when each side was stimulated at the wrist and upper forearm, but were doubled on the affected side for stimulation proximal to the lesion. In this case the increased latency must be attributed to decreased conduction velocity in the affected segment of nerve and it can be presumed that the same explanation holds in the carpal tunnel syndrome.

Pressure lesions of the ulnar nerve occur less commonly in the hand and tend to be situated distal to the branch to the hypothenar muscles (Seddon, 1952). One case of deep branch neuritis of the right ulnar nerve with sparing of hypothenar muscles was examined. The ulnar nerve was stimulated at three points and action potentials recorded in the first dorsal interosseous and abductor digiti minimi (the latter path being 4 cm. shorter by surface measurement). Control measurements on the right median nerve, to the opponens pollicis, resembled those of the ulnar branch to the abductor digiti minimi. The conduction velocity of fibres to the abductor digiti minimi was normal and compared closely with that of the median nerve of the same limb but there was a marked delay peripheral to the wrist in the fibres to the first dorsal interosseous muscle (Table II).

TABLE II

CONDUCTION TIME IN ULNAR DEEP-BRANCH NEURITIS

Right Ulnar				Right Median	
First Dorsal Interosseous		Abductor Digiti Minimi		Opponens Pollicis	
cm.	m.sec.	cm.	m.sec.	cm.	m.sec.
38	19 : 30*	34	8·5	32	8
21	15 : 26*	17	4	—	—
12	12 : 23*	8	3	5·5	3·5

*The initial unit and a later recognizable unit. Each was delayed in comparison with the abductor digiti minimi and each unit maintained the same temporal dispersion.

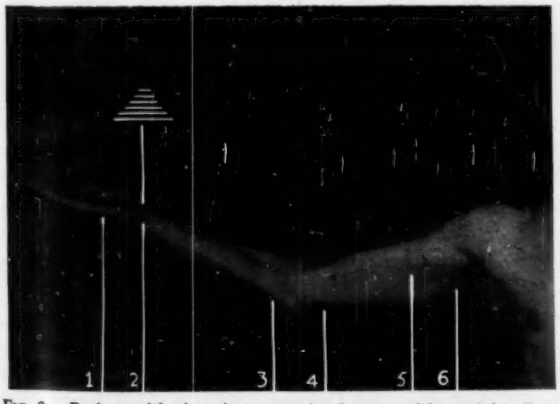


FIG. 2.—Patient with chronic traumatic ulnar neuritis at right elbow, illustrating method used. Needle electrode in abductor digiti minimi (1) and stimulating cathode applied in turn to points 2, 3, 4, and 5 over the ulnar nerve. Stimulating anode over upper arm (6) and earthed electrode just proximal to needle electrode.

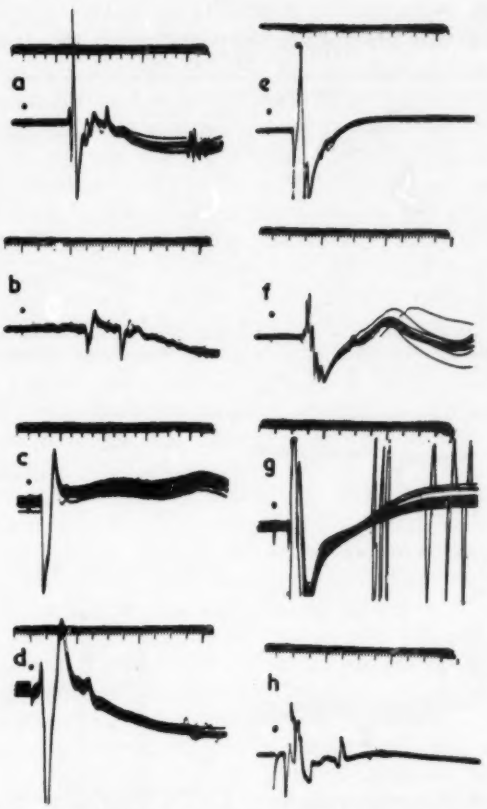


FIG. 3.—Case shown in Fig. 2 *a-d* right ulnar, *e-h* left ulnar nerve. Recording from abductor digiti minimi of each hand. Time marks 1 and 5 m.sec. (scale varies).

	R. Ulnar Nerve		L. Ulnar Nerve	
	cm.	m.sec.*	cm.	m.sec.*
Axilla	43·5	20·5	46·5	10
Above elbow	37	17·5	39	8·7
Below elbow	17	5	17·5	3·5
Wrist	6·5	2·5	6·5	2·5

*Latencies measured on larger scale records than those reproduced.

Five patients with carpal tunnel syndrome were re-examined after operative decompression of the median nerve (Table III and Fig. 4). The shortest latency in the abductor pollicis brevis or opponens pollicis from supramaximal stimulation just proximal to the flexor retinaculum was compared with the pre-operative measurement. In Cases 7 and 8 the nerve causing most pain was decompressed though conduction velocity was less impaired than on the other side. In Case 3 the latter had been previously decompressed. Two cases showed no change in conduction time one month after operation and no further examination was obtained. In the other three cases the latency of response returned to normal though in one case the prolongation was increased during the first fortnight and recovery was not measurable until two months after operation.

TABLE III

EFFECT OF OPERATIVE DECOMPRESSION IN CARPAL TUNNEL SYNDROME

Case	Operated Nerve		"Control" Nerve (m.sec.)
	Before (m.sec.)	After (m.sec.)	
1	11	6·5* 5·5† 5·0‡	4
2	8	10 * 8·5† 6·5‡	4
3	7	4·5†	6·5
7	5	5 †	14
8	8·5	8·5†	10

*2 weeks after operation. †4 weeks after operation.
‡8-12 weeks after operation.

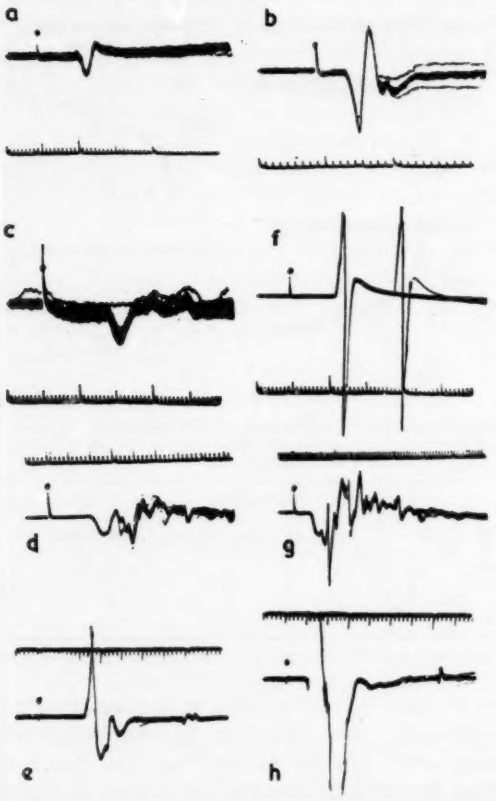


FIG. 4.—Case 1, right carpal tunnel syndrome. Effect of decompression.

a-b. Left median nerve to abductor pollicis brevis (*a* = elbow; *b* = wrist).

c-h. Right median nerve to abductor pollicis brevis (*c-e* = elbow; *f-h* = wrist).

Compare *c*, *f* (pre-operative) with *d*, *g* (2 weeks) and *e*, *h* (3 months). Note progressive reduction in latency and temporal dispersion of muscle action-potential, and repetitive firing (*f*). (cf. Table II).

Time marks 1 and 5 or 10 m.sec. (scale varies).

Delay in Slower Fibres.—The configuration of the summated action-potential of muscle, whether recorded by surface electrodes or as in the present study, suggests that motor units are not quite synchronously innervated by a supramaximal shock applied to a point on the motor nerve. The summated muscle action-potential broadens and decreases in amplitude as the stimulating electrode is moved proximally along the nerve (Bolzani, 1954). The asynchrony increases in the carpal tunnel syndrome (*e.g.*, Fig. 4) so that the muscle action potential may last for 50 m.sec. or longer (normal about 20 m.sec.) and become highly polyphasic. The disintegration may allow individual motor units to be recognized later than the shortest latency unit, particularly when a needle electrode is used. After decompression of the nerve the scatter of latencies is reduced and the summated muscle action potential regains its normal form (Fig. 4). The possibility suggests itself that the increased latency to the earliest-firing unit in the ischaemic nerve is due to block of only the largest (and presumably fastest) fibres but this would not explain the great increase of the total duration of the complex. Furthermore, in some cases of carpal tunnel syndrome, as in experimental ischaemia of a segment of nerve (Kugelberg and Cobb, 1951), the whole complex is delayed without much alteration in its configuration. Thus it seems likely that decreased conduction velocity affects all sizes of fibre.

Repetitive Firing.—In a considerable experience of this type of investigation the author has never recorded repetitive firing of motor units in normal subjects, but this phenomenon was present in seven of the 15 patients with carpal tunnel syndrome (Figs. 4 and 5). The occurrence of this is readily recognized by observation of the oscilloscope screen, or by listening to the monitoring loudspeaker. In Fig. 4, where the whole complex within range of the needle fired twice during a single sweep (of the 10 superimposed), or in Fig. 5, where a single (threshold) unit is readily identifiable by its shape, the nature of the "double" or "treble" unit recorded is readily recognized, but repetitive firing occurring during the dispersed complex described above can be difficult to recognize, especially if the stimulus is not truly supramaximal. The superimposition of successive records is valuable since the repetitive firing occurs with only a fraction of the stimuli and its period shows considerable variability (Fig. 5).

Table I shows that bilateral conduction delay in motor fibres was common, suggesting that the lesion may be bilateral though subjective symptoms are only unilateral. Indeed the abnormality of conduction may be worse on the side with least sensory disturbance and repetitive firing was sometimes found in the muscles supplied by the median nerve on that side. An excellent example of repetitive firing (probably of the F wave) (Magladery and McDougal, 1950) (Fig. 3 g) was recorded from the

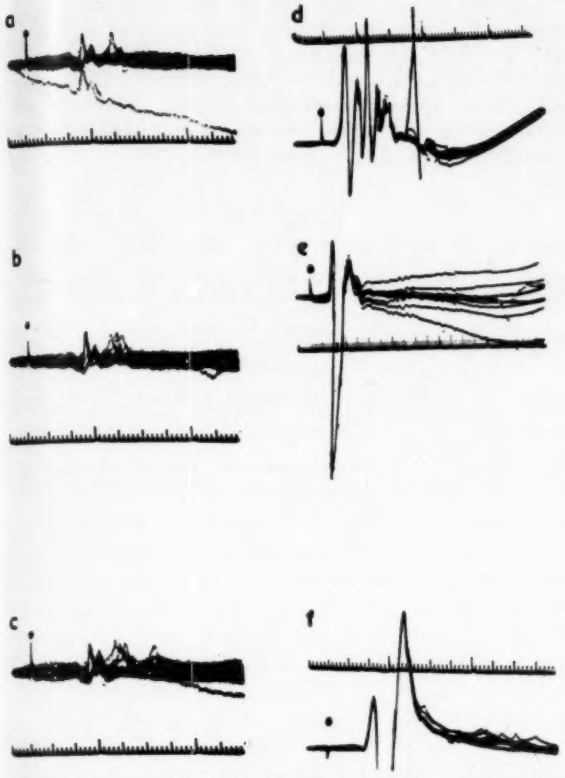


FIG. 5.—*a*, *b*, *c*, consecutive records of 10 superimposed responses from abductor pollicis brevis in carpal tunnel syndrome. A single unit, evoked by threshold stimuli, has a recognizable shape enabling its occasional repetitive firing (once or twice) to be identified. The period is variable (*b*, *c*) and also in *d* and *f* (from other cases), but remarkably constant in *e*. Time marks 1 and 5 or 10 m.sec.

apparently unaffected side in the case of chronic traumatic ulnar neuritis. No explanation for this is apparent.

Discussion

The present investigation was suggested by a personal re-investigation of the effects of local compression of a peripheral nerve as previously described by Kugelberg (1946) and Kugelberg and Cobb (1951). These authors have shown that during the application of compression the conduction velocity in motor nerve fibres progressively decreases in the compressed segment only and that during compression and for a short time afterwards repetitive firing of motor nerve fibres occurs either spontaneously or as the result of electrical stimulation. Kugelberg (1946) suggested that a similar phenomenon in sensory fibres would explain paraesthesiae and pain occurring in certain circumstances.

It seemed probable that the same changes would be found in pathological processes associated with localized ischaemic changes in peripheral nerve. The expected modification of conduction and the presence of repetitive firing were observed. These changes have not hitherto been recorded in natural pathological states. The observation that conduction is normal distal to the lesion and the recovery after operation make it unlikely that the slow conduction occurs in regenerating fibres. The results of this investigation have not been tabulated as conduction velocities calculated from the distances and latencies because the possible error involved in the calculation is considerable. The length-measurement made on the surface is very approximate and the surface area of the stimulating cathode (diameter 1 cm.) is relatively large and its zone of effective influence in the tissues unknown but probably larger, particularly with the supramaximal stimulation considered essential. Thus the " effective cathode " at the nerve may be more than a centimetre in either direction from the centre of the electrode. Time measurement is probably not accurate to more than 0·5 m.sec., as it is often difficult to define exactly where the recorded action potential begins to deviate from the base line. A rough calculation shows that with a " measured length " of nerve of 20 cm. and " measured time " of 5 m.sec. the calculated velocity of conduction could be 35-47 m.p.s. Even then the calculated figure represents an average based on the assumption of constant velocity of conduction in the measured length of nerve whereas in fact there is evidence that normal peripheral nerve conducts with decreasing velocity as it extends peripherally and this difference is exaggerated by cooling of the periphery (Baxt and Helmholtz, 1870). It is submitted that the method of comparison of corresponding nerves of each upper limb, stimulated in the same way at symmetrical points and recorded under the same conditions of temperature, provides satisfactory criteria of difference from the normal without introducing quantitative concepts with high inherent fallacies.

The present investigation was not designed to test the reliability of these changes as a diagnostic examination. To assess the significance of normal findings and the correlation of the electrical signs with the symptoms in the early case of carpal tunnel syndrome, a long-term follow-up of cases in which no conduction abnormality was detected and sequential examination of early untreated cases would be necessary. Nevertheless, the incidence of positive findings in the small number of patients investigated suggests that the changes described in this paper will be of value as a confirmatory test.

Summary

Slowed conduction has been demonstrated in the presumed ischaemic section of the median nerve in 11 of 15 cases of carpal tunnel syndrome (bilateral

in four cases) and in three cases this was shown to return towards normal after operative decompression.

Repetitive firing of motor units after single shock stimulation was present in seven of 15 cases. Increased temporal dispersion of the summated action-potential of a muscle supplied by the compressed nerve returned to normal after decompression.

In one patient with chronic traumatic neuritis of the ulnar nerve at the elbow the slowed conduction was shown to be confined to the damaged segment of nerve.* In a patient with neuritis of the deep branch of the ulnar nerve it was demonstrated that the branch to abductor digiti minimi escaped the conduction block which was found in fibres to the first dorsal interosseous muscle.

*Since this paper was written the findings have been confirmed in three further cases.

I should like to thank Dr. W. A. Cobb and Mr. H. Morton for providing facilities and technical assistance, and Drs. E. A. Carmichael, R. Gilliatt, and M. Kremer for permitting me to examine their patients. Discussions with Dr. G. Dawson were most helpful. The work was done during the tenure of an M.R.C. fellowship in clinical research.

References

Baxt, N., and Helmholtz, H. (1870). *Mber. preuss. Akad. Wiss. Berlin*, p. 184.
Bolzani, L. (1954). *Schweiz. Arch. Neurol. Psychiat.*, **74**, 148.
Brain, W. R., Northfield, D., and Wilkinson, M. (1952). *Brain*, **75**, 187.
——, Wright, A. D., and Wilkinson, M. (1947). *Lancet*, **1**, 277.
Kugelberg, E. (1946). *Brain*, **69**, 310.
——, and Cobb, W. A. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 88.
Kremer, M., Gilliatt, R. W., Golding, J. S. R., and Wilson, T. G. (1953). *Lancet*, **2**, 590.
Magladery, J. W., and McDougal, D. B. (1950). *Bull. Johns Hopk. Hosp.*, **86**, 265.
Seddon, H. J. (1952). *J. Bone Jt Surg.*, **34B**, 386.
Walshe, F. M. R. (1951). In Feiling, A. *Modern Trends in Neurology*. Butterworth, London.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 281.

ISCHAEMIC AND POSTISCHAEMIC PARAESTHESIAE IN POLYNEURITIS

BY

E. W. POOLE

From the Department of Neurology, Radcliffe Infirmary, Oxford

Paraesthesiae consequent on peripheral nerve compression or general limb ischaemia have attracted interest for over a century (Bastien and Vulpian, 1855), but their value in the study of nervous disease remains little explored. In a recent study (Poole, 1956) the paraesthesiae provoked in normal subjects by a standard ischaemic test were investigated in order to provide a background against which pathological conditions could be judged. This report concerns the responses elicited in subjects with polyneuritis.

Many features of paraesthesiae responses suggest their possible usefulness in the study of diffuse peripheral nerve disorders such as polyneuritis. The tingling, or " pins-and-needles ", which occurs during limb ischaemia, ischaemic paraesthesiae (I.P.), and which follow circulatory release, post-ischaemic paraesthesiae (P.I.P.), arises in sensory mechanisms subserving distal areas of the limb, and the larger fibres are probably mainly concerned. Such a preferential involvement is seen clinically, in polyneuritis from many causes, and experimentally, as in vitamin deficiency (Swank, 1940; Horwitt, Liebert, Kreisler, and Wittman, 1946), and intoxications, *e.g.*, with triorthocresyl phosphate (Cavanagh, 1954). There is also evidence suggesting that such tests of iterative responsiveness may provide a sensitive index of nerve function. Sensation returns rapidly to normal after a period of limb ischaemia (Lewis, Pickering, and Rothschild, 1931), but paraesthesiae may not be elicited again to their full extent for many hours (Merrington and Nathan, 1949). Further, paraesthesiae may be lacking in certain areas in normal subjects without manifest sensory impairment, or be entirely absent as in the elderly (Poole, 1956). Thus it might be supposed that paraesthesiae responses should be readily disturbed in polyneuritis thereby providing a sensitive index of involvement and recovery. This theory was tested in two ways. Repeated examinations were made in conditions where some degree of recovery might be expected so that the significance and sensitivity of any paraesthesiae changes would be established by their subsequent regression along with general sensory recovery. Secondly, the responses in these and in other cases (either static or not available for follow-up) were compared with those elicited in comparable normal subjects (Poole, 1956). Since recovery was usually very slow this latter approach was more generally applicable. Fortunately the responses in normal subjects and in those with polyneuritis proved sufficiently uniform and divergent to render this method satisfactory, thus facilitating the simple clinical application of such tests.

Material and Methods

The cases studied are presented in three groups.

Group I.—This consisted of eight cases of acute toxic polyneuritis of unknown aetiology.

Group II.—This group contained 11 cases, the majority with polyneuritis of more chronic type, either of unknown aetiology or in association with other diseases. Included also are brief notes of the responses in less certain cases of polyneuritis in diabetes and porphyria, and in one case of Charcot-Marie-Tooth disease.

Group III.—This was five cases of megaloblastic anaemia, only one with a manifest polyneuritis. Neuropathies of various aetiologies have been included but a comprehensive survey of the effects of any single agent is not attempted.

Examinations were performed under warm, quiet circumstances wherever possible, and every effort made to avoid fatigue, the sensory testing being broken up with many intervals for rest and the ischaemic tests carried out when the subject was fresh or at an interval after sensory testing. The development and present status of the sensory and motor symptoms were recorded with special reference to the presence of spontaneous or " contact " paraesthesiae-like sensations. The usual clinical assessments of motor, reflex, and sensory functions were augmented by the use of graded nylon hairs to assess tactile perception (stimulus, t, = bending thrust (g.) hair radius (mm.), weighted needles to provide standard pricking stimuli (Marshall, 1953), and tuning forks activated to standard degrees to assess vibration

perception (Poole, 1954). Attempts were made to determine both the density and extent of sensory impairment so that serial examinations might give some objective measure of progress. Defects were judged against responses in more normal parts of the limb, performances in follow-up examinations, and experiences in normal subjects tested similarly.

Ischaemic tests in the upper limb were performed and assessed as previously described (Poole, 1956). Care was taken to ensure that the limb was warm and the interdigital cleft temperature was recorded. Special attention was paid to changes in any spontaneous or contact paraesthesiae initially present. In some cases observations were also made on the degree of postischaemic muscle twitching in the first dorsal interosseous muscle, a motor response analogous to P.I.P. but less readily induced (Kugelberg, 1944, 1948). An interval of at least 24 hours separated repeated tests on the same limb. In some instances lower limb occlusions were achieved without excessive discomfort, and the results have been noted. The technique was essentially similar to that for the arm, but the subject was lying flat and a cuff of 30 cm. × 17 cm. at 200 to 250 mm. Hg pressure was employed high up on the thigh. The lower limb initially seemed, because of its greater susceptibility to disease processes, a more fruitful field for study, but the tests caused too much discomfort, appeared relatively less productive of P.I.P. than in the upper limb, and probably carried a greater risk of vascular damage. In all, over 120 tests were performed.

The duration of provocative ischaemia was important in determining the ensuing P.I.P. and muscle twitching. The presence of heightened muscle tenderness, the possible harmful effects of prolonged ischaemia, and the desire to provide a delicate assessment all favoured the minimal occlusion normally entirely adequate. A 10-minute upper arm occlusion was found to fulfil these requirements for P.I.P. in all except a minority of the elderly (Poole, 1956) and was then generally adopted. However, in the cases first studied occlusions were fixed individually as the greatest time between 10 and 20 minutes tolerated in the initial test. Later examinations of comparable duration might thus be readily achieved as muscle tenderness subsided with general recovery. However, the lack of P.I.P. norms for these varying occlusions created unnecessary difficulties in interpretation, though these could usually be overcome by reference to norms for the duration of P.I.P. in 10-minute tests (Poole, 1956). Prolonged occlusions had advantages in assessing postischaemic muscle twitching.

The timing of the initial and follow-up tests varied depending on the clinical state, progress, and availability for examination, some cases being followed for over two years. In acute disorders the initial test was performed only when the process had been clearly improving or stationary for at least one week to minimize the risk of aggravating the affection. This unfortunately left the earliest changes undefined, but it seemed wisest to postpone this until experience in the later phases established the precise features of interest. In fact, no adverse effects of occlusion tests were encountered and the responses in a limb serially examined over many months were similar to those in the comparably affected opposite limb occluded finally for the first time.

Results

Group I (Acute Toxic Polyneuritis).—In all cases I.P. were absent or not clearly present, and P.I.P. less marked than in normal subjects, even in some instances despite apparently complete subjective and objective sensory recovery. The occurrence of spontaneous paraesthesiae-like impressions in the course of the disease did not favour the production of I.P. or P.I.P. Limited observations on post-ischaemic muscle twitching suggested that such responses were also depressed. Brief notes of the cases (in approximate order of age) follow. Normal responses against which these results were judged have been detailed previously (Poole, 1956), but it may be noted that clear I.P. were elicited in all young (< 31 years) and the majority (72%) of older normal subjects (31-60 years); while distinct P.I.P. exceeding two minutes in duration were provoked by 10-minute occlusions in all except a minority of the oldest subjects (> 60 years).

Case 1.—This 16-year-old schoolgirl (R.I. 179909) became ill with a heavy cold and 10 days later (August 27, 1953) developed a severe generalized paralysis requiring the use of intermittent positive pressure respiration to some extent for four weeks. Moderate distal sensory impairment was established when recovery permitted at the end of the first month. She made a complete clinical recovery over the next seven months and ischaemic tests on the right arm gave the following results (left essentially similar):—

Weeks after onset	8	9	11	15	28	105
Minutes of occlusion	10	15	10	10	13	8·5
I.P. (intensity)	0	0	0	0	0	++
P.I.P. (intensity)	0	0	0	±	+	++
Duration of P.I.P. (min.)	0	0	0	< ½	1·7	2

Muscle power had completely recovered (in the upper limbs) by the 28th week (possibly by the 15th week). The deep reflexes could be just elicited at the 28th week, but even at the 105th the triceps jerks remained depressed. Sensory recovery was incomplete at the eighth week when doubtful spontaneous or contact paraesthesiae were still present from time to time and sensory testing suggested a minimal defect in 2-point discrimination; but at later tests there was no subjective or objective impairment.

As is shown above, I.P. were not elicited till the final examination when they appeared approximately normally. Postischaemic paraesthesiae were similarly impaired, being at first entirely absent, and later dull and transient despite peripheral stimulation by tapping and pressure. However, in the final test (unfortunately limited to eight and a half minutes' occlusion by discomfort) distinct, sharp P.I.P. were perceived—a response which might be taken as normal, though there were some minor

atypical features in that the impressions were more marked in the palm than in the fingers, and peripheral stimuli (tapping and pressure) were required to produce sharp impressions.

Paraesthesiae responses were clearly severely impaired by the polyneuritis. Their recovery lagged behind that of ordinary sensation and was associated with the return of deep reflex responses.

Case 2.—This aircraftman, aged 21, developed respiratory infection on May 22, 1954, followed within a week by facial, palatal, and general muscle weakness, with paraesthesiae and sensory impairment in the limbs. Improvement was clearly evident one and a half weeks after the onset of nervous symptoms, and recovery was nearly complete after 10 weeks. Ischaemic tests during recovery gave the following results:—

Weeks after onset	6	8	11	
Minutes of occlusion	13(L)	13·5(L)	14(L)	10(R)
I.P. (intensity)	0	0	+	+
P.I.P. (intensity)	0	±	+	+
Duration of P.I.P. (min.)	0	< ½	4·5	2·3

At the sixth week moderate general limb weakness persisted, with muscle tenderness and areflexia. The hands felt stiff and heavy, and sensation was abnormal, with a general " woolly " feeling and tingling on contact to a level 2 to 3 in. above the wrist. Testing showed slightly impaired tactile perception (3t) on the digits, but no change in pricking stimuli. Perception of passive movement at the distal interphalangeal joints was slightly defective as was vibration sense also. Two-point discrimination on the finger pulps showed occasional errors at ½ cm. separation. A 13-minute occlusion produced no paraesthesiae. His usual contact paraesthesiae were dulled relative to the other limb after four minutes and entirely eliminated by 12 minutes, only returning completely some 15 minutes after circulatory restoration (possibly partly by 3 minutes).

At the eighth week the upper limb power was almost normal, though the areflexia persisted. Sensation was not quite normal in that paraesthesiae on contact still persisted to some degree. Sensory examination showed minimal defects on the distal phalanges only. A 13·5 minute occlusion again gave no I.P. or P.I.P. However, there were some vague tingling impressions in the later stages of occlusion, and transient " beating " feelings in the fingers on circulatory release unaffected by peripheral stimulation.

At the 11th week upper limb power was essentially normal, and some deep reflexes were sluggishly elicited. Sensation was considered normal, and examination showed none of the previous minimal changes. Occlusions of 14 minutes (on the side usually tested) and 10 minutes (on the opposite) both gave slight I.P.; and P.I.P. also followed in the fingers, more severe and long-lasting after the longer occlusion. These P.I.P. were atypical in being only faintly spontaneously apparent and requiring peripheral stimulation to evoke sharp impressions. No muscle twitching was seen.

This case showed a progressive, though incomplete, restoration of normal paraesthesiae responses (at this age), defects persisting despite apparently complete sensory recovery. Paraesthesiae-like impressions occurring as a result of the disease did not predispose to induced paraesthesiae with ischaemia and were readily depressed by circulatory occlusion. The lack of postischaemic muscle twitching was also suggestive of a defect in iterative responses, since occlusions of 15 minutes (Kugelberg, 1944) and even 10 minutes (Poole, 1956) provoked twitching in the majority of young normal subjects.

Case 3.—This schoolboy, aged 14 (R.I. 198793) had severe limb, bulbar, and facial paresis, but less severe sensory impairment. Muscle tenderness prevented ischaemic tests until late in the recovery, which was rapid once initiated. Two 10-minute occlusions were performed eight and 11 weeks after the onset, when spontaneous paraesthesiae had ceased and the upper limbs showed no subjective or objective sensory abnormality except a minimal defect in vibration perception at the terminal phalanges. Slight muscle paresis persisted, and the deep reflexes were absent at the first test and elicited doubtfully at the second. Moderate residual sensory and motor defects were clearly evident in the lower limbs. In both ischaemic tests I.P. were absent, but moderate P.I.P. (duration three minutes) and muscle twitching were provoked. The P.I.P. were relatively short-lived for this age, and only in the later tests were aggravated by peripheral stimuli. Lack of I.P. was clearly a significant departure from normal responses, and the short P.I.P. were in keeping with this defect (Poole, 1956).

Case 4.—This 17-year-old schoolgirl (R.I. 182462) developed, in association with glandular fever, a severe polyneuritis requiring artificial respiration to some extent for two weeks. Paraesthesiae and sensory defects were well marked, more severe on the left side. She made a very rapid recovery within six weeks of the onset, and ischaemic tests gave the following results:—

Weeks after onset	2	4		6	
Minutes of occlusion	10 (R)	12 (R)	12 (L)	8 (R)	8 (L)
I.P. (intensity)	?	0	0	0	0
P.I.P. (intensity)	+	++	+	++	+
Duration of P.I.P. (min.)	? < 3	2·2	1·8	2·2	2·5

The first test was performed in difficult circumstances during artificial respiration when there was probably some degree of alkalosis and nitrogen retention. Spontaneous paraesthesiae were present, and it was difficult to be certain if I.P. were induced, but P.I.P. followed to some extent. At the fourth week, despite rapid improvement with doubtful return of reflexes, considerable weakness persisted. Spontaneous paraesthesiae had largely gone, but the hands felt unnatural, especially the left, and there was slight impairment of all forms of sensation extending up to the wrist, more marked on the left. Occlusion tests (12 minute) produced no I.P. but short-lived P.I.P. followed in the fingers bilaterally, very feeble and curiously delayed in onset on the left.

At the sixth week only slight paresis persisted distally and the deep reflexes could be clearly elicited. Sensation was not quite normal in the fingers, especially on the left side; a minimal defect was demonstrable in light touch on the left finger tips, and in the appreciation of passive movement at the terminal interphalangeal joints. Bilateral occlusions (unfortunately limited to eight minutes) provoked no I.P.; but moderate P.I.P. followed, less marked and delayed in onset on the left.

It was difficult to compare the initial test with later ones because of biochemical disturbances. In later tests the lack of I.P. was a consistent departure from normal, and P.I.P. were also reduced, at least in the earlier test. There was less impairment of P.I.P. than in many other cases, and it was noteworthy that the clinical recovery was rapid and the deep reflexes soon returned.

Case 5.—This labourer, aged 39 (R.I. 193125), developed severe motor and sensory defects in the limbs, the former recovering slowly almost completely over the next 15 months, but the latter tending to persist. Ischaemic tests performed during recovery gave the following results:—

Weeks after onset	6	9	13		60	
Minutes of occlusion	15 (L)	14 (L)	14 (L)	10 (R)	10 (L)	10 (R)
I.P.	0	0	0	±	±	±
P.I.P.	? 0	? 0	0	0	+	+
Duration of P.I.P. (min.)	? < ½	? < ½	0	0	1-2	2-3

Spontaneous or contact paraesthesiae were present only at the first test, but moderate sensory defects persisted throughout. The motor power had returned almost to normal by the final test, but the deep reflexes remained absent. As is apparent, defects in I.P. and P.I.P. persisted throughout. Faint or doubtful I.P. were elicited only in the final tests. Some doubt arose as to whether there were any faint P.I.P. in the thermal post-ischaemic impressions in the early tests, but it was only in the final examinations that definite P.I.P. resulted. However, even these were abnormal in that there was little spontaneous activity, the impressions being mainly provoked by tapping and pressure on the fingers, and this response was very delayed in onset. Faint I.P. referred to areas with distinct residual sensory defects were not observed in other cases, and the prognostic significance of this is not yet apparent. Postischaemic muscle twitching was not seen after a 14-minute occlusion, suggesting similar defects in motor iterative responses.

Case 6.—This farmer, aged 42 (R.I. 145424), developed an acute polyneuritis two weeks after a sore throat with fever, but had been in brief contact with organic mercurial compounds six weeks previously. Motor involvement was severe but short of a degree requiring respiratory assistance; sensory impairment was relatively mild in the arms, more severe in the legs. Recovery after an initial relapse was moderately rapid in the arms, but slight motor and sensory defects were still evident in the legs 18 months later. Ischaemic tests during this period gave the following consistently abnormal results:—

Weeks after onset	5	7	9	11	18	27	75
Minutes of occlusion	9·5	10	11	10	10	10	10
I.P. (intensity)	0	?0	0	0	0	0	0
P.I.P. (intensity)	0	0	±	±	0	0	+
Duration of P.I.P. (min.)	0	0	? < 1	? < 1	0	0	1

Thus I.P. were not elicited except doubtfully in the second test in association with considerable discomfort. Postischaemic paraesthesiae were not provoked with any certainty till the final test, and even this short response was only faintly spontaneous and required peripheral stimulation to provoke distinct pricking. These impaired responses were obtained despite the return of the upper limb to subjective and objective sensory normality by the 27th week, if not before. An associated change was depression of the deep reflexes, but at the final examination biceps and supinator jerks were distinctly elicited.

Cases 7 *and* 8.—Two elderly women (aged 52 and 62) who had had severe motor but slight distal sensory involvement (in the upper limbs) were examined when there was little, if any, subjective or objective impairment, though spontaneous or contact paraesthesiae were present occasionally in the finger tips. The deep reflexes were still not elicitable. Bilateral occlusion tests, limited by muscle tenderness to eight minutes, gave no I.P., P.I.P., or muscle twitching. These results were not necessarily a departure from normal at this age, though in keeping with usual polyneuritis responses. They show (as was apparent in most cases) the importance of having standard tests of minimal duration for application to conditions with heightened muscle tenderness.

Group II (Chronic, Recurrent, and Other Neuropathies).—In the majority of cases defects in I.P., P.I.P., and muscle twitching of the type found in Group I were observed. Thus only brief notes of the cases are presented except where possibly significant additional points arose.

Case 9.—Recurrent acute polyneuritis in a man aged 21 (R.I. 212192) without any precipitating cause. A 10-minute ischaemic test five weeks after the recurrence in the presence of moderate sensory defects gave no I.P., P.I.P., or muscle twitching. "Contact" paraesthesiae-like sensations which were constantly present were readily depressed by ischaemia and totally abolished within seven minutes of occlusion, returning, at least in part, within one minute of circulatory release. At the stage of ischaemia where such sensations were lacking the feeling in the occluded limb was considered to be more natural than in the unoccluded, as has been observed in other cases.

Case 10.—Polyneuritis in a woman aged 32 (R.I. 189300). In November, 1953, this housewife developed, insidiously, symmetrical limb weakness with paraesthesiae and numbness in the fingers, feet and calves. Improvement was evident three months later and the paresis and reflex responses recovered (incompletely) over the next 16 months. Because of dense distal sensory

defects this case was studied specially to determine if at any stage of recovery paraesthesiae could be provoked in fibres yet to (or about to) re-establish full functional peripheral connexions with the numb areas on analogy with amputee results where paraesthesiae can be provoked in the phantom by stump ischaemia (Weddell and Sinclair, 1947; Merrington and Nathan, 1949; Poole, 1954). This might be of prognostic value, but, as experience with other cases showed, the readiness with which paraesthesiae responses were disturbed made it much more likely that their restoration would lag behind sensory recovery.

Ischaemic tests (15) were performed in the upper and lower limbs from the fifth to the nineteenth month after the onset. Ischaemic paraesthesiae, P.I.P., and muscle twitching were all provoked and the responses increased during recovery. Of more interest was the limited distal reference of paraesthesiae and their modification by peripheral stimulation. The dense distal sensory defects extended to a fairly sharp level 1-2 cm. from the finger tip with no definite defect in more proximal phalanges save a slightly impaired vibration perception in the early stages. Ischaemic paraesthesiae, even when prominent, were confined to the palm. Post-ischaemic paraesthesiae extended little further than the proximal phalanges in earlier tests (16-18 minute occlusions) but later spread more distally towards the numb areas (10-16 minute occlusions). Peripheral stimuli of pressure on the proximal phalanges markedly aggravated the P.I.P. but on the distal phalanges had no effect. In proximal parts of the intermediate phalanges pressure could provoke P.I.P. not spontaneously apparent and, in the later stages of recovery, this response could be elicited slightly more distally. However, at no stage could paraesthesiae be provoked in areas of manifest sensory impairment nor in immediately adjacent proximal zones. Unfortunately sensory recovery was too limited to establish any order of recovery of sensation and paraesthesiae in the terminal parts. Nevertheless, the pattern of paraesthesiae reference on the limb strongly suggested that the recovery of paraesthesiae responses lagged behind that of sensation as ordinarily assessed.

Case 11.—Polyneuritis in a french-polisher aged 51 (S. 6758) developing insidiously without apparent cause, though toxic occupational factors must be considered. Motor and sensory defects were manifest subjectively and objectively in the legs, but the arms were never subjectively affected and examination disclosed only reflex depression and slight weakness without sensory impairment. Ischaemic tests 10 over a two-year period presented a uniform picture. Ischaemic paraesthesiae were absent and P.I.P. elicited transiently and feebly with 15-minute occlusions, those of 13 minutes and 10 minutes being ineffective. No postischaemic muscle twitching was seen. Apart from clearing of any weakness the clinical status of the arms remained unchanged, the reflex depression persisting. Comparable observations were made in the lower limb where gradual improvement in paresis and sensory defects was evident. Ischaemic paraesthesiae were consistently absent but short-lived P.I.P. were elicited by a 14-minute occlusion in the late recovery stages whereas previously this had produced no response. It was noteworthy that upper limb paraesthesiae responses remained consistently out of keeping with the normal even though there had been no apparent sensory affection of these parts.

Case 12.—Polyneuritis with steatorrhoea in a woman aged 53 (R.I. 7143): symmetrical distal weakness and moderately severe sensory impairment developed insidiously in this long-standing case of steatorrhoea under vitamin and dietary treatment. Six ischaemic tests over a two-month period during which the clinical state showed little change gave consistent results: I.P. were absent; P.I.P. were not provoked by 10-minute occlusions but those of 14 minutes gave faint, dull, thrusting sensations in the fingers for two to three minutes. Since distinct sensory impairment was evident to mid-forearm level, the presence of even these dull P.I.P. was possibly surprising in comparison with other cases. It was noteworthy that, from the subsequent deterioration of this case, the lesions were probably not confined to the peripheral nerves (*vide* Smith, 1955).

Cases 13 *and* 14.—Chronic polyneuritis not certainly due to an underlying carcinoma in two women aged 65 and 68 (R.I. 193735; R.I. 186606): the younger had little upper limb sensory impairment, the elder severe; both had spontaneous paraesthesiae at times. In neither did repeated ischaemic tests of 10 to 20 minutes' duration over several months produce I.P., P.I.P., or muscle twitching.

Case 15.—Motor neuropathy with carcinoma of the lung in a man aged 61 (S. 10239): over a few months this man developed severe symmetrical wasting and weakness, maximal distally, without evident fasciculation or clear sensory impairment (allowing for slight ageing change in vibration perception). Deep reflexes were still elicitable. A 10-minute occlusion produced no I.P., P.I.P., or muscle twitching. This result was in keeping with a minority of normal responses at this age, and also with the responses seen in polyneuritis. However, this was also seen in subjects with similar extreme wasting from motor neuron disease.

Cases 16 *and* 17 (*Diabetic Neuropathy*).—Two diabetics (aged 58 and 61) had sensory defects and depressed reflexes in the lower limbs but no sensory impairment (or subjective abnormality) in the upper limbs, though the reflexes were also depressed or absent. A 10-minute upper arm occlusion in the older gave no I.P. or P.I.P. In the younger, though both were induced by an 11-minute occlusion, they were referred predominantly to the palm and wrist rather than to the fingers, as is usual (for P.I.P. at least). The P.I.P. of less than two minutes' duration were shorter-lived and more feeble than might have been expected normally. These limited results, though possibly not greatly out of keeping with a minority of normal responses, tended towards the defects in polyneuritis and suggested paraesthesiae tests might contribute to the study of diabetic neuropathies.

Case 18.—Porphyria with neuropathy in a woman aged 20 (R.I. 168851): this girl, who had had symptoms

of porphyria for one to two years and slight distal limb weakness for some months, rapidly developed symmetrical distal paresis with foot and wrist drop. However, the paresis did not spread, the reflexes were said to be unaltered, and no sensory symptoms or defects were recorded. When seen for ischaemic tests one month later, the paresis had been improving for two weeks; only moderate distal weakness persisted (predominantly in the dorsiflexors), the deep reflexes were elicited, and sensation appeared normal. A 14-minute occlusion gave clear I.P. and P.I.P. The normality of this result contrasted with cases of polyneuritis, but the pattern of nervous involvement was also different.

Case 19.—Charcot-Marie-Tooth disease in a woman aged 27 (R.I. 194340): this schoolteacher had severe wasting of all muscles distal to the upper third of the forearm with depressed or absent deep reflexes, and moderate sensory impairment distal to the wrist. Bilateral 10-minute tests gave no P.I.P. or muscle twitching (though there was little muscle to observe). No I.P. were induced on the right, but on the left some tingling began in the forearm four minutes after the occlusion and was thought to spread distally to involve all the fingers. There was no obvious reason for this asymmetry, and indeed the power and sensation were possibly better preserved on the right. Though lack of paraesthesiae might be attributed to sensory defects, muscle wasting in motor neuron disease has been found associated with similar defects.

Group III (Megaloblastic Anaemia).—In two patients in whom detailed observations and follow-up were possible, paraesthesiae responses were initially defective but returned towards normal with B_{12} therapy, thus resembling acute toxic polyneuritis. These results are presented first, and then brief notes of three other patients in whom only limited studies could be made.

Case 20.—Polyneuritis and subacute combined degeneration with pernicious anaemia (R.I. 185685): this 65-year-old housewife with severe anaemia had had numbness, paraesthesiae, weakness, and unsteadiness in the legs for many months, and numbness and paraesthesiae in the hands for a few weeks before admission. Examination disclosed a mild polyneuritis in the arms. There was slight distal weakness, increased muscle tenderness, and depressed, though not absent, deep reflexes. Textures felt odd to the touch and there were occasional paraesthesiae in the fingers; but no great sensory impairment was demonstrable, there being only slight defects in tactile (3t) and vibration perception at the terminal phalanges, and in the detection of passive movement at the terminal interphalangeal joints. However, two points could not be discriminated with complete accuracy at 1 cm. separation on the pulps. The lower limbs showed considerable objective and subjective sensory and motor disturbances distally with clear evidence of cord lesions. Ischaemic tests were performed in both upper and lower limbs before therapy and over the ensuing seven months. The arm results were as follows:—

Weeks, relative to B_{12} therapy	$-\frac{1}{2}$	$+\frac{1}{2}$	+1	+2	+3	$+5\frac{1}{2}$	$+7\frac{1}{2}$	+12	+28
Minutes of occlusion	12	12	14	17	21	20	20	20	10
I.P. (intensity)	0	0	0	0	0	0	±	+	±
P.I.P. (intensity)	0	0	0	0	0	+	++	++	+
Duration of P.I.P. (min.)	0	0	0	0	0	3-4	4	4	1·5
Haemoglobin (%)	37	46	50	86	—	85	89	—	99

As is seen, I.P. and P.I.P. were not elicited before therapy nor in the succeeding month, even though there was considerable subjective improvement in that spontaneous paraesthesiae disappeared and only the finger tips felt slightly odd. Moreover, objectively, the power increased, reflexes became more definite, and sensory testing showed none of the previous defects except a minimal one in vibration perception. During the second month distinct, though mild, P.I.P. were elicited for the first time, referred mainly to the palm and proximal phalanges. The upper limbs were considered subjectively normal except for a very doubtful finger tip change in sensation without objective defects. During the third month when the hands were entirely natural slight I.P. were also induced (though only in the one test referred to the fingers), and increased P.I.P. were elicited referred to all phalanges. With the final standard 10-minute test I.P. were not clearly present but P.I.P. were induced throughout the hand and were aggravated by pressure and movement.

Parallel studies in the leg showed, in the first month, an absence of I.P. and P.I.P. in occlusions of up to 24 minutes' duration despite the presence of spontaneous paraesthesiae-like sensations. However, from the second month onwards, P.I.P. consistently followed 20-minute occlusions and after the third month I.P. were also apparent even though distinct sensory defects persisted along with a spastic paresis (and absent ankle jerks).

The recovery of normal paraesthesiae responses in the upper limb clearly lagged behind the improvement in the blood count and followed more closely the symptoms of subjective sensory normality. The initial lack of distal reference was possibly significant in the pattern of recovery. The appearance of I.P. later than P.I.P. was in keeping with the long duration of provocative ischaemia and the usual findings in polyneuritis. The absence of clear I.P. in the final test may be a reflection of the feebleness of the sensations normally at this age and the less satisfactory examination conditions in the final follow-up. In the lower limb, despite persistent residual defects, there was a distinct recovery presumably due to the regression of the polyneuritis, but it was not possible to ascertain if the residual sensory defects were entirely determined by cord lesions.

Case 21.—Post-gastrectomy megaloblastic anaemia in a man aged 55 (R.I. 188738): a partial gastrectomy for

gastric ulcer was performed in 1941 and 12 years later investigation disclosed a megaloblastic anaemia with deficient B_{12} absorption. There were no nervous symptoms, and motor, reflex and sensory examinations were entirely normal apart from doubtfully increased muscle tenderness and a minimal defect in vibration perception in the legs and possibly in the arms. Ischaemic tests on the left arm before and after B_{12} therapy gave the following results:—

Weeks, relative to B_{12} therapy	$-\frac{1}{2}$	+2	+3	+48
Minutes of occlusion	14	19	$16\frac{1}{2}$	10
I.P. (intensity)	0	±	+	++
P.I.P. (intensity)	0	+	++	++
Duration of P.I.P. (min.)	0	2	> 5	2·7
Haemoglobin (%)	48	68	75	105

Thus, whereas both I.P. and P.I.P. were lacking before therapy, these were elicited with increasing vigour following B_{12} administration. Parallel studies in the lower limb showed very similar changes. Ischaemic paraesthesiae and P.I.P. were lacking initially but P.I.P. were feebly evoked after two weeks' therapy and to a greater extent after three weeks when I.P. were also reported. Thus, as in cases of polyneuritis, defects in paraesthesiae could occur in the absence of objective or subjective sensory changes and, with B_{12} therapy, recover in association with improvement in the blood count, without obvious change in the sensory status.

Case 22.—Mild pernicious anaemia in a woman aged 56 (R.I. 110330) without symptoms or signs of nervous lesions. A 10-minute occlusion before therapy (haemoglobin 68%) gave doubtful I.P. and faint P.I.P. (duration less than 2 minutes) referred patchily to digits III and V.

Case 23.—Severe pernicious anaemia in a woman aged 68 (R.I. 77218) without symptoms or signs of nervous lesions: a 10-minute occlusion before therapy (haemoglobin 40%) provoked no I.P. but minimal (or doubtful) P.I.P. followed, amounting to slight throbbing in the terminal pulps for two to three minutes, unaffected by peripheral stimuli.

Case 24.—Mild obscure megaloblastic anaemia in a woman aged 50 (R.I. 189298), not secondary to manifest steatorrhoea: there were no symptoms indicating nervous involvement but she was a dull witness. The deep reflexes were all sluggish and one plantar response equivocal, but there was no certain sensory impairment. Five occlusions of 16 to 20 minutes in the upper and lower limbs during one month's B_{12} therapy (when the haemoglobin level rose from 70 to 80%) provoked no paraesthesiae or muscle twitching.

These three cases showed responses either less than or of the minimal type found in normal subjects. While it was clearly unwise to apply "normal" criteria in any strict fashion in the absence of complete follow-up, reduced iterative responses were in keeping with other cases of this series.

Discussion

This study confirms the view that paraesthesiae responses are severely disturbed in polyneuritis. Such depression of iterative responses provides a sensitive index of preceding affection, as is shown in many features such as the persistence of paraesthesiae defects in the absence of subjective or objective sensory impairment, the regression of such defects without obvious change in sensory status, and the failure of paraesthesiae to be elicited in normal areas proximal to affected parts (*e.g.*, in the palm when only the finger tips are clinically abnormal). The influence of age on normal responses is of value in interpreting the results, and indeed the defects in polyneuritis are those to be expected from the type of change seen in ageing (Poole, 1956) and in repeated limb ischaemia (Weddell and Sinclair, 1947; Merrington and Nathan, 1949). Thus, as in ageing, I.P. are more frequently totally lacking than "10-minute" P.I.P., but in such circumstances the latter are usually relatively short-lived. Since 10-minute P.I.P. are much more intense than I.P. this relationship suggests some common factor impairing the most responsive elements or producing a general decrease in iterative activity. It is noteworthy that the polyneuritis results are in keeping with the general working rule proposed from ageing studies that, if I.P. are clearly present, P.I.P. will follow a 10-minute occlusion, a rule which also appears to hold in cerebral and cord lesions (Poole, 1954).

Observations on muscle twitching, though limited, support the view that such iterative responses are also impaired, even though the only associated clinical defect might be depression of deep reflexes. Muscle twitching was never unequivocally provoked in the absence of P.I.P., thus preserving the normal relationships between sensory and motor responsiveness (Kugelberg, 1944 and 1948; Skoglund, 1942; Poole, 1956), but electromyographic studies would be needed for conclusive observations in this field.

In megaloblastic anaemia decreased paraesthesiae responses without manifest sensory impairment may be due to subclinical neuropathy from B_{12} deficiency, but the influence of anaemia *per se* has not been established in these preliminary studies. However, tests in 13 subjects with secondary anaemia (haemoglobin 55-74%) showed little sign of impaired responses (Poole, 1956), and in the two megaloblastic cases studied most completely (20 and 21) the return of normal paraesthesiae was related more to the severity of the initial nervous lesions than to the restoration of the blood count. Nevertheless, the frequent occurrence of paraesthesiae as symptoms of severe anaemia and the inhibiting effect of recurrent ischaemia on I.P. and P.I.P. both suggest that disturbed iterative responses might well be found in

severe anaemia if occlusion tests can be safely applied.

From the clinical viewpoint the present results are of interest not only in defining the presence and progress of neuropathies in many diseases (intoxications, vitamin deficiencies, alcoholism, malignant disease, diabetes, leprosy, etc.) but also in the study of different types of peripheral nerve dysfunction. Whereas severe depression of paraesthesiae responses appears characteristic of diffuse polyneuritis, normal or exaggerated responses may occur in focal lesions, *e.g.*, carpal tunnel syndrome (Gilliatt and Wilson, 1953), in general hyperexcitable states, *e.g.*, tetany (Kugelberg, 1944), and possibly also in interstitial neuritis since prematurely-occurring I.P. have been described in sciatica (Marshall, 1952). It is noteworthy that gross depression of paraesthesiae responses in association with slight sensory defects (or spontaneous paraesthesiae-like sensations) has not been found to be the rule in preliminary studies of cord and cerebral lesions (Poole, 1954). The prognostic value of paraesthesiae assessments remains uncertain. Little has been found to favour the possibility that paraesthesiae might be provoked in proximal parts of recovering fibres and thereby indicate potential recovery (*vide* Case 10). With few limited (but perhaps significant) exceptions recovery of iterative responsiveness lagged behind full clinical sensory recovery in the area concerned.

It is not possible to discuss the many problems raised by this study but two may be briefly noted. One feature is that spontaneous paraesthesiae or similar sensations evoked by surface contact do not favour the production of I.P. or P.I.P., though they are obviously influenced by peripheral ischaemia. As has been pointed out, this forms a contrast with other conditions where spontaneous paraesthesiae are a feature. The sensory mechanisms involved in such spontaneous sensations may not be those participating in ischaemic iterative responses, but their susceptibility to ischaemia (and activation by pressure) makes this likely. Another problem is the precise basis for the defects in paraesthesiae. In polyneuritis (as in ageing) decreased responses may occur without manifest sensory impairment, just as reflex depression may persist despite " full " motor recovery. Indeed these associated paraesthesiae and reflex defects might suggest a common basis, that is, an afferent basis for reflex depression and a proprioceptive share in paraesthesiae responses. Obviously, defects in paraesthesiae occurring in the absence of clear sensory deficits may be due to the crudity of the latter and the delicacy of the former assessments in detecting a functional loss of fibres. However, the question arises whether there is a stage at which induced iterative fibre activity may be impaired though function via end-organ stimulation is relatively intact. Slight disturbances in myelination might provide a basis for this, though many other changes have to be borne in mind. The decreased responses in polyneuritis represent a trend towards the motor type of reaction to ischaemia (Skoglund, 1942; Kugelberg, 1944 and 1948) and the factors determining the accommodation and repetitiousness of various fibres are ill-defined. Electrophysiological studies in clinical and experimental neuropathies may clarify this and circumvent some of the difficulties inherent in clinical sensory investigations.

Summary

Ischaemic and postischaemic paraesthesiae have been studied in cases of polyneuritis and megaloblastic anaemia. The responses elicited successively over many months have been contrasted with the clinical recovery, and compared with those found in normal subjects. These observations confirm that such paraesthesiae are profoundly disturbed in polyneuritis and thereby provide a sensitive index of involvement and recovery. Postischaemic muscle twitching responses appear similarly depressed. The significance of these defects in iterative responses is briefly discussed.

I wish to thank Dr. W. Ritchie Russell and Dr. C. W. M. Whitty for permission to study patients under their care, and for advice and criticism of the text. Some of the cases were kindly provided by Prof. L. J. Witts, and Drs. A. M. Cooke, E. M. Buzzard, J. Kidd, and P. Mallam. Financial assistance from a Henry Goodger Scholarship is gratefully acknowledged.

References

Bastien, J. B., and Vulpian, A. (1855). *Gaz. méd., Paris*, 3 ser, 10, 794.
Cavanagh, J. B. (1954). *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 163.
Gilliatt, R. W., and Wilson, T. G. (1953). *Lancet*, **2**, 595.
Horwitt, M. K., Liebert, E., Kreisler, O., and Wittman, P. (1946). *Science*, **104**, 407.
Kugelberg, E. (1944). *Acta. physiol. scand.*, **8**, Suppl. 24.
—— (1948). *Arch. Neurol. Psychiat. (Chicago)*, **60**, 140.
Lewis, T., Pickering, G. W., and Rothschild, P. (1931). *Heart*, **16**, 1.
Marshall, J. (1952). *Journal of Neurology, Neurosurgery and Psychiatry*, **15**, 242.
——, (1953). *Clin. Sci.*, **12**, 247.
Merrington, W. R., and Nathan, P. W. (1949). *Journal of Neurology, Neurosurgery and Psychiatry*, **12**, 1.
Poole, E. W. (1954). Unpublished observations.
—— (1956). *Journal of Neurology, Neurosurgery and Psychiatry*, **19**, 148.
Skoglund, C. R. (1942). *Acta. physiol. scand.*, **4**, Suppl. 12.
Smith, W. T. (1955). *Excerpta. med. (Amst.)*, Sect. VIII, **8**, 860.
Swank, R. L. (1940). *J. exp. Med.*, **71**, 683.
Weddell, G., and Sinclair, D. C. (1947). *Journal of Neurology, Neurosurgery and Psychiatry*, **10**, 26.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 289.

THE PUPILLARY CHANGES IN THE HOLMES-ADIE SYNDROME

BY

G. F. M. RUSSELL

From the Neurological Unit, the Northern General Hospital, Edinburgh

Widely varying pupillary abnormalities are in clinical practice often grouped under the heading of the Holmes-Adie syndrome. Adie (1932) described the complete form of the disorder as comprising the typical tonic pupil, with its characteristic delayed reaction to convergence and the loss of some of the tendon reflexes, whereas in the incomplete form he included those cases in which the reflexes were normal, or the pupillary disturbance was atypical (as in the fixed pupil of ophthalmoplegia interna). Alajouanine and Morax (1938) state that no two pupils are identical, and they agree with Lowenstein and Friedman (1942) that between the typical tonic and syphilitic pupils all kinds of intermediary changes may be seen. They suggest, moreover, that pupillotonia is not a fixed condition, but may follow on a paralysed pupil and even precede an Argyll Robertson pupil. A similar evolution in which the fixed pupil of ophthalmoplegia interna becomes typically tonic is described by Rothmann (1903), Axenfeld (1919), Reitsch (1925), and Adie (1932). Adie, on the other hand, says that the tonic pupil may suddenly become dilated and fixed, but there are no definite recorded instances of this. Holmes (1931) describes the course of events in a patient who, over a period of 17 years, developed anisocoria, then a left pupillary lesion, and finally a lesion of the right pupil.

In order to unify the many pupillary variants and to understand how the disturbance develops, studies were made of the effect of procaine block of the stellate ganglion and of the reaction of the pupil to drugs. In this way, additional light was shed on the pathogenesis of the lesion.

Case Reports

The clinical findings are summarized in Table I. Four cases merit more detailed description, because they illustrate the multiplicity of pupillary abnormalities encountered in the syndrome.

Case 1.—A young single woman suddenly sensed a blurring of the vision of the left eye, and on looking in a mirror she noticed that the left pupil was somewhat larger than the right. Next morning she found that the left pupil had enlarged even further, and thereafter it remained fully dilated. Examination two months later revealed a large pupil, fixed to light and convergence, with paralysis of accommodation in the same eye and a reduction of visual acuity to J.7. Eleven months after the onset of symptoms she was again able to read J.1, but accommodation from distant to close vision required 13 seconds. The pupil still failed to respond to both light and convergence, and the tendon reflexes remained normal. In view of the development of delayed accommodation this case of ophthalmoplegia interna was included in the series.

Case 2.—This young girl had suffered from an intermittent divergent heterotropia since the age of 5, but had compensated for it fairly well until now. During the course of her clerical work she suddenly noticed a dimness in the vision of the left eye, and her attention was drawn to an enlargement of the pupil on that side. Thereafter, the tendency to divergence of the eyes became accentuated and she had to close the left eye while at work to avoid troublesome diplopia. Examination showed a left tonic pupil and absent knee and ankle jerks. Sixteen months later (October 2, 1955), while she was reading, the right eye became blurred, and to continue reading she had to close that eye and revert to fixation with the left eye. She was examined within two days of this relapse, and it was found that the right pupil was enlarged and reacted poorly to light and accommodation. Visual acuity on that side remained at J.1, but 15 seconds were required for accommodation from a distance, and the near point was 25 cm. All tendon reflexes were absent excep. the right biceps jerk. Frequent examinations over the next few days revealed progressive paralysis of accommodation. On October 6 she could only read J.3 with the right eye, and on October 15 vision was restricted to J.8 and the near point increased to 58 cm., while distant vision remained relatively unaltered. At the same time the pupil became further enlarged, fixed to light, and only slightly responsive to accommodation. Her heterophoria was now decompensated and she developed an intermittent divergent squint for close vision and a convergence insufficiency. With a plus 3 lens in front of the right eye she could see J.1, but the left eye became divergent, whereas without glasses she depended on the left eye and the right eye deviated outwards.

Case 10.—A man of 34 had attended an ophthalmic department in September, 1954, complaining of a

TABLE I
SUMMARY OF CLINICAL FINDINGS

Case No.	Age (yr.)	Sex	History	Features of Pupil(s)	Size at Rest (mm.)	Size after convergence	Size after Stellate Ganglion Block	Time for Relaxation after Constriction (sec.)	Size at rest	Size after convergence†	Size at rest	Size after pilocarpine	Cocaine 3% (mm.)	Homatropine ¼% (mm.)	"Mecholyl" 2½% (mm.)	Tendon Reflexes	W.R.
1	33	F	Sudden blurring of vision (December, 1954)	Fixed irregular pupil with tonic accommodation	9	9	9	—	1	1·13	Nil	Nil	Nil	Normal	Negative in C.S.F and blood
2	25	F	Sudden blurring of vision of left eye in 1954; similar occurrence in right eye in 1955	Bilateral changes affecting both pupil and accommodation; paralytic on the right and tonic on the left	R. 5½	4½	4½	11	1·2	1·5	→7½	→8	→5	All absent except right B.J.	Negative in C.S.F. and blood
					L. 8	2½	3	40	2·5	3·0	→10	→9	→4		
3	56	F	Incidental finding; episode of blurred vision in 1924	Oval tonic pupil with normal accommodation	5	3½	3½	12	1·3	1·8	→5	→7	→3½	Absent T.J.s, K.J.s, A.J.s	Negative in blood
4	34	F	Incidental finding (1955)	Bilateral irregular tonic pupils with tonic accommodation on left	R. 5	3½	—	4	—	—	→6	→7	Nil	Absent T.J.s, K.J.s, A.J.s	Negative in blood
					L. 4	3	—	11	1·4	2·0	→5½	→5½	Nil		
5	36	F	Incidental finding (1954)	Irregular tonic pupil; normal accommodation	3½	2½	—	22	1·4	1·8	→4½	→5	→2½	All absent	Negative in blood
6	56	F	Incidental finding (1956)	Bilateral irregular pupils; normal accommodation	R. 3	2	—	18	1·5	1·8	→4½	—	—	Absent A.J.s	Negative in blood
					L. 3½	2	—	8	—	—	→5	—	—		
7	69	F	Incidental finding (1955)	Bilateral changes; pupils irregular; accommodation slow on left	R. 3	2	—	6	—	—	→3½	→6	→2½	T.J.s, K.J.s, A.J.s absent; S.J.s sluggish	Negative in C.S.F. and blood
					L. 2½	2	1½	20	1·5	2·2	→5	→5	→1½		
8	19	F	Sudden onset of pain in the right eye (1955); enlargement of the left pupil noted at that time	Bilateral irregular pupils with more markedly tonic reaction on the left; accommodation normal	R. 3½	2½	—	5	—	—	→4½	→7	→2½	Absent K.J.s, A.J.s	Negative in C.S.F. and blood
					L. 7½	4½	4½	20	1·5	2·2	→8	→8	→4½		
9	55	F	Incidental finding (1955)	Bilateral irregular tonic pupils; delayed accommodation	R. 4½	3	3	20	1·5	2·3	→7½	→7	→4	All absent	Negative in C.S.F. and blood
					L. 5	2½	—	7	—	—	→6½	→7	Nil		
10	35	M	Sudden onset of blurred vision	Fixed left pupil (1954); one year later developed a tonic pupil and slow accommodation	5	2½	3	20	1·9	2·3	→7½	→9	—	Absent S.J.s, A.J.s; K.J.s sluggish	Negative in blood
11	49	M	Incidental finding (1955)	Irregular tonic pupil; delayed accommodation on the right	7	3	2½	45	1·9	2·3	→8	→8	→4½	A.J.s absent	Negative in C.S.F. and blood
12	37	F	Incidental finding (1956)	Bilateral irregular tonic pupils; marked delay of accommodation	R. 4	2	2	40	2·2	2·5	→5½	→5½	→3	Absent B.J.s, T.J.s, K.J.s, A.J.s	Negative in blood
					L. 5½	3	—	10	—	—	→7	→7	→4½		
13	36	F	Incidental finding (1955)	Bilateral irregular tonic pupils; normal accommodation	R. 3½	2	—	30	—	—	→5½	→5½	→3	Absent K.J.s, A.J.s, and R. B.J., S.J.	Negative in C.S.F. and blood
					L. 5½	2	2	48	2·2	2·7	→7	→7	→2½		
14	51	M	Incidental finding (1955)	Oval tonic pupil with slow accommodation; ipsilateral ptosis and facial anhidrosis	4	3½	4	10	*	*	Nil	→8	Nil	A.J.s sluggish	Negative in C.S.F. and blood

† The size of the resting pupil is measured before the pilocarpine test, and therefore often differs from the average reading at rest.
* These indices are not valid owing to the permanent sympathetic lesion.

B.J., S.J., T.J., K.J., A.J. = biceps, supinator, triceps, knee, and ankle jerk.

sensation of glare in the left eye which had developed suddenly. At this time the left pupil was found to be dilated and fixed to light and convergence. When seen 16 months later, his symptoms had subsided and the pupil was irregular and typically tonic, taking 20 seconds to dilate after relaxation of convergence. During a medical examination in 1939 it had been noted that the tendon reflexes in the legs were sluggish or absent.

Case 14.—A 51-year-old dock worker was admitted to hospital with pneumonia, where it was noted that he had a left-sided ptosis and an oval enlarged pupil which reacted only slightly and sluggishly to light and convergence. He maintained that the ptosis had been present all his life and that his father, now dead, had also had a drooping upper eyelid. Sweat tests showed anhidrosis on the left side of the face, and the ptosis was therefore ascribed to a lesion of unknown causation in the sympathetic pathway proximal to the bifurcation of the common carotid artery. Clearly, this could not alone account for an irregular, enlarged, and poorly reacting pupil. The following evidence was obtained for including the patient in the series of tonic pupils: pupillary dilatation to 6½ mm. resulted when he was kept in total darkness for 40 minutes, and after exposure to bright daylight the pupil took three minutes to return to a diameter of 3½ mm. This was, therefore, a rare example of the natural occurrence of a tonic pupil with a sympathetic lesion.

Many of the clinical features emphasized by Graveson (1949) were encountered in this series. Irregularity of the pupils was a constant finding, and bilateral pupillary changes were often present (Cases 2, 4, 6, 7, 8, 9, 12, and 13). In Cases 4, 7, and 8, the second pupil showed only slightly delayed relaxation (4, 6, and 5 seconds respectively), but these times were held to be significant in view of the accompanying irregular pupillary outline. The abnormal pupil was not necessarily enlarged: in nine instances it measured 4 mm. or less in diameter, and in one it was only 2½ mm. Adie suggests that the stimulus of convergence is stronger than that of light, quite apart from whether or not the nervous pathways conveying these reactions are anatomically distinct. This is certainly borne out by the behaviour of abnormal pupils in which constriction to convergence is always greater than constriction to light or accommodation. An exception to this rule may be found in patients with an insufficiency of convergence, often associated with an heterophoria, as in Case 2. The effect of weeping on the tonic pupil was observed in one patient who was depressed (Case 9). As noted by Adie, Holmes, and Graveson, crying caused pupillary constriction followed by the slow relaxation. Adie (1932) and Kennedy, Wortis, Reichard, and Fair (1938) say that loss of the upper limb reflexes is uncommon, but it was found in nine of the 14 patients investigated, the triceps jerks being most commonly affected. In two patients, moreover, all the reflexes were absent.

There is often a more than superficial similarity between Holmes-Adie and Argyll Robertson pupils. Confusion is most likely to arise when the pupils are small, for a delay in constriction and dilatation is naturally more difficult to detect when the range of movement is slight. This problem remains one in the interpretation of signs, the pathogenesis and aetiology of the two kinds of pupils being probably quite distinct. Certainly there is no evidence of a syphilitic basis in any of the cases reported in this series.

Methods of Investigation

Procaine Block of the Stellate Ganglion.—This was done on 11 abnormal pupils in 10 patients to find out whether an over-activity or a lesion of the sympathetic nervous system played a part in the pathogenesis of the condition. In over-activity, a procaine block of the sympathetic nervous system would nullify at least some of the anomalies of the tonic pupil, so that special attention was directed to the resulting change in pupillary size and the effect on pupillotonia. In a lesion of the sympathetic nervous system, on the other hand, further interruption by procaine block would not cause any alteration in the size of the pupil. The stellate ganglion on the side of the abnormal pupil was infiltrated with 5 ml. of 1% procaine hydrochloride according to the method advocated by Moore (1954), using an anterior cervical approach. (There are only two records in the literature of the effect of a stellate ganglion block on the Holmes-Adie pupil (Barré and Klein, 1934; Alajouanine and Morax, 1938) and these are at variance with each other.)

In the 11 pupils tested, pupillary constriction occurred to a widely varying degree (Table I and Fig. 1). Where the reduction in the size of the pupil was slight or absent, the effectiveness of the procaine block was ascertained by the development of ptosis, conjunctival injection, and facial anhidrosis. When necessary, a sweat test was performed immediately after the procaine injection, using quinizarin 2:6 disulphonic acid powder (Burroughs and Wellcome) as an indicator. In Case 1, for instance, facial anhidrosis was demonstrated when the pupil remained fully dilated. This result was the same as that found with stellate ganglion block in normal patients where the pupil is paralysed by 2% homatropine. Pupillary constriction after interruption of the sympathetic depends on the action of functioning parasympathetic fibres, and its extent is thus a measure of the degree of parasympathetic preservation, which can be expressed by the ratio

$$\frac{\text{Size of the pupil at rest}}{\text{Size of the pupil after stellate ganglion block}}$$

Fig. 1 shows that the size of the pupil reached after the procaine block matched closely that resulting from convergence under resting conditions, so long as this movement could be maintained adequately. It is simpler,

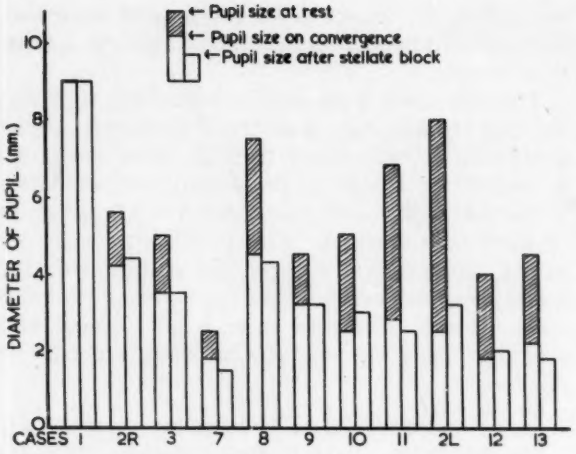


FIG. 1.—For each patient, the size of the pupil reached after stellate ganglion block approximates to that resulting from convergence under resting conditions (measured immediately before the block).

therefore, to assess parasympathetic sparing by the fraction

$$\frac{\text{Size of the pupil at rest}}{\text{Size of the pupil after convergence}}$$

The slowest reacting pupils showed the greatest degree of miosis after stellate ganglion block. The range of contraction in response to convergence became diminished thereafter, so that timing by the naked eye of constriction and relaxation was rendered extremely difficult. Accordingly, a cinephotographic record was made of the tonic pupil before and after the procaine block. The left pupil of Case 2 was chosen as it became markedly reduced in size after the block. Illumination presented no problem, for this pupil did not react even to the brightest light. The patient was asked to look at a close object, and after the pupil showed no further constriction, she was told to look at the reflection of a distant light in a mirror placed close to the camera lens. The film was exposed at a rate of 16 frames per second, so that the time taken by these pupillary movements could be measured with great accuracy. Fig. 2 shows the response of this pupil to accommodation before and after the sympathetic block, the amplitude of contraction becoming reduced from 1·9 mm. to 0·9 mm. The time taken for the subsequent return to resting size was 23 seconds in the first instance, and 13 seconds after stellate ganglion block. When these values are equated with the reduced range of movement, it is seen that there is no alteration in the speed of pupillary relaxation; this is also borne out by the comparable slopes of the two curves.

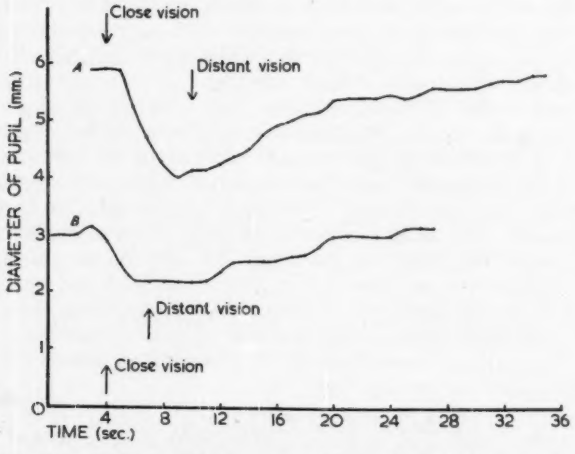


FIG. 2A.—Response of the pupil before stellate ganglion block; there is a delay of 23 sec. for return to resting size after accommodation.

FIG. 2B.—Response of the pupil after stellate ganglion block; the rate of dilatation remains unaltered.

The Conjunctival Instillation of Drugs.—Two drops of the chosen solution were instilled from the same ungraduated dropper into each eye. By this method the reaction of the two pupils could be compared, which was of great value when one of the pupils was normal.

Drugs with a Sympathetic Action.—Cocaine hydrochloride (3%) and adrenaline hydrochloride (0·1%) were used as a further test of sympathetic function. Jaffe (1950) has shown that with sympathectomized pupils the mydriatic effect of cocaine is lost as long as the site of the lesion is outside the central nervous system. As can be seen from Table I, cocaine caused a normal mydriatic response in every instance except in Case 1, where further dilatation was not possible, and in Case 14 where there was a known sympathetic defect. This effect was not excessive, however, for when the affected pupil was smaller than its normal or relatively normal fellow, this relation of size remained unaltered (Table II). Jaffe also claims that in the presence of a post-ganglionic sympathetic lesion, instilled adrenaline causes pupillary dilatation. No such reaction was found in any of the cases.

TABLE II

COMPARISON OF THE EFFECT OF DRUGS BETWEEN THE PUPILS OF INDIVIDUAL PATIENTS

Case	Cocaine 3%		Homatropine ½%	
	Abnormal Pupil (mm.)	Normal or Less Affected Pupil (mm.)	Abnormal Pupil (mm.)	Normal or Less Affected Pupil (mm.)
3	4→5	3½→6	4½→7	7→8
4	4½→5½	5→6	4½→5½	5½→7
5	3½→4½	5½→6½	3½→5	4½→7
6	3→4½	3½→4½	—	—
12	4→5½	5½→7	3→5½	5½→7

Parasympathomimetic Drugs.—"Mecholyl" (2½%), pilocarpine nitrate (1%), and eserine sulphate (0·25%), in the given concentrations, cause various responses in the normal eye. Eserine produces a maximal pupillary contraction, whereas "mecholyl" (acetyl B methyl choline) is without any effect; pilocarpine occupies an intermediate position.

When tested on the abnormal pupil, these substances showed the same relative potency, but the resulting miosis varied greatly from case to case.

The response to eserine was of particular interest in Case 2, where the markedly tonic left pupil was compared with the right one, unaffected at the time. On

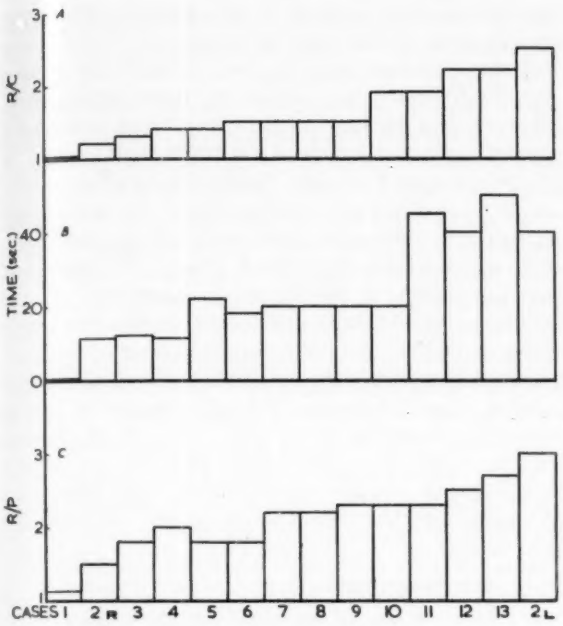


FIG. 3A.—R/C is the value of the fraction

$$\frac{\text{Size of pupil at rest}}{\text{Size of pupil on convergence}}$$

(*i.e.*, index of remaining parasympathetic function.)

FIG. 3B.—Time (sec.) taken for relaxation of pupil after constriction.

FIG. 3C.—R/P is the value of the fraction

$$\frac{\text{Size of pupil at rest}}{\text{Size of pupil after pilocarpine}}$$

(*i.e.*, index of sensitivity.)

The cases are graded according to the degree of remaining parasympathetic function (A = greatest on the right, and least on the left), which is proportionate to the delay in relaxation (B) and the sensitivity of the pupil (C).

the right side a constriction from 3 to 2 mm. was obtained, whereas the left pupil, initially the larger, became reduced from 7½ to 1½ mm. within half an hour, and this miotic effect persisted after the right pupil had returned to its resting size. In addition, spasm of accommodation occurred on the left side only, with resulting ocular pain and blurring of vision, the visual acuity changing from J.1 to J.8. In contrast, a concentration of 0·5% eserine was required to cause constriction of the pupil in Case 1 from 9 to 4 mm.

The action of " mecholyl " was tested in 19 abnormal pupils. In 14 of these, pupillary constriction resulted as shown in Table I, but five pupils remained unaltered in size. Again, there was a marked variation in the effect of pilocarpine, from an absence of any response to a marked sensitivity, which was assessed by comparing the resting size of the pupil with that after maximal constriction (Table I and Fig. 3). Increased sensitivity is denoted by high values of the fraction

$$\frac{\text{Size of the pupil at rest}}{\text{Minimal size of the pupil after pilocarpine}}$$

This index of sensitivity is reliable only in cases where the pupil's reaction to light is absent or sluggish; otherwise uncontrolled variations in illumination alter its value.

Homatropine Hydrobromide (0·5%).—Moore (1931) states that pupillary dilatation to atropine is always full in the Holmes-Adie syndrome, in contrast with the incomplete effect of the drug on the Argyll-Robertson pupil. Alajouanine and Morax go further and say that the pupillary dilatation to homatropine is precocious and excessive. However, when a weak solution of homatropine was used in this series, the relationship of size between the pupils was preserved as a rule. Where the abnormal or more severely affected pupil was originally enlarged, dilatation was full, but where it was the smaller of the two, it did not reach full mydriasis with this concentration of the drug (Table II).

Discussion

The Functional Disturbance in the Holmes-Adie Pupil.—In considering the pathogenesis of the lesion, the relative role of the sympathetic and parasympathetic must be assessed.

(1) *The Sympathetic Innervation of the Pupil.*—Several writers, including Adie, hold that at least some of the clinical features of the syndrome can be attributed to excessive or deficient sympathetic action. Most support is given to the theory of overaction of the sympathetic nerves in various sites (Garcin and Kipfer, 1936; Lowenstein and Friedman, 1942). It was to test this theory that studies were made by means of procaine block of the stellate ganglion.

The effect of a temporary interruption of the sympathetic on pupillary size varied from a marked miosis in Case 2L to a lack of any demonstrable constriction in Case 1. The pupil was therefore kept enlarged by sympathetic activity only in certain cases; where the dilatation remained virtually unaltered after stellate ganglion block, a different mechanism must have been involved. Further observations were made on the tonic reaction of the pupil under conditions of sympathetic block. It was noted that a certain reduction occurred in the time taken for this reaction, but the point at issue was whether any change took place in the actual rate of pupillary constriction and dilatation over what had become a smaller range of movement. Cine/photographic measurements in Case 2L showed that this rate remained virtually unaltered after the block (Fig. 2). In other words, the sympathetic innervation is not responsible for the speed of pupillary movement, but partially governs the total time taken for relaxation by controlling the degree of dilatation.

The opposing view of sympathetic insufficiency has been held by other authors. Alajouanine and

Morax (1938) attribute the excessive lability of the tonic pupil to its liberation from nervous control, sympathetic as well as parasympathetic. The occasionally associated ptosis (Alajouanine and Morax; Moore, 1931) seems to favour their view. Moreover, Graveson (1949) tentatively turns to such an explanation for the not infrequent finding of normal-sized or even miotic pupils. McKinney and Frocht (1940) and Scheie (1940) maintain, however, that the pupillo-dilator mechanism is intact, and confirmation of this is afforded by the present investigation.

In the first place, procaine block of the stellate ganglion resulted in pupillary constriction in every case where such constriction was possible (as shown by a preserved reaction to convergence). Secondly, the reaction of the pupil to cocaine and to adrenaline eye-drops remained normal. These two results provide ample proof of remaining sympathetic function, and were obtained with even the smallest pupils in the series (Cases 4, 5, 6, 7, 12, and 13). The only exception was Case 14, where ptosis and facial anhidrosis were present on the side of the tonic pupil. There the sympathetic lesion affected the sweat fibres and must, therefore, have involved the pathways proximal to the bifurcation of the common carotid artery—probably preganglionic fibres. In fact, this patient presented a picture similar to that obtained after stellate ganglion block in the other cases. Possibly this is a coincidental association of the tonic pupil and Horner's syndrome, since ptosis is a rare finding, and facial anhidrosis has never been described in the Holmes-Adie syndrome.

(2) *The Parasympathetic Innervation of the Pupil.*—Most workers agree that a parasympathetic lesion is at least partly responsible for the clinical features of the pupillary abnormality (Behr, 1921; Adie, 1932; McKinney and Frocht, 1940; Scheie, 1940; and Leathart, 1942). Thus the usual absence of the reaction to light and the impairment of the reaction to convergence can be ascribed to such a lesion, and the slow constriction of the tonic pupil may also be a result of parasympathetic weakness.

From what has already been said, it can be understood why the pupil often fails to contract fully on convergence. Not infrequently, however, the paradoxical situation arises in which the constriction is greater than normal, or " tonic " in character, and it may be accompanied by spasm of accommodation when this function is also affected (Reitsch, 1925; Holmes, 1931; Alajouanine and Morax, 1938). Slowness of constriction can be explained by parasympathetic weakness, but another cause must be sought for the occasional excessive amplitude of the movement. The answer is provided by observing the reaction of the pupil to drugs.

In his classical account, Adie stated that eserine and mydriatics were normal in their action. Alajouanine and Morax, on the other hand, reported a precocious or exaggerated reaction to a variety of pharmacological agents, including eserine, pilocarpine, cocaine, and homatropine. In the present studies, cocaine and adrenaline were normal in their effect, and homatropine dilated the pupil, but not excessively. Evidence of sensitivity of the abnormal pupil to the cholinergic drugs was sometimes noted; for example, pupillary constriction was sometimes excessive in amplitude or persisted unduly long, so that the abnormal pupil, usually the larger, became the smaller of the two. It must be pointed out, however, that this sensitivity was not always evident. The reaction to pilocarpine was the easiest to assess, and the index of sensitivity, as expressed by the ratio

$$\frac{\text{Size of the pupil at rest}}{\text{Minimal size of the pupil after pilocarpine}}$$

was found to vary through a wide range (Fig. 3).

The most striking fact which emerges is that there is an approximate correlation between the degree of sensitivity to pilocarpine, the residual parasympathetic function and the time taken for pupillary relaxation. In other words, sensitivity to the cholinergic drug was found to be greatest when the " tonic " reaction was most obvious, the term " tonic " referring to both the range of movement and its delay. Conversely, where pupillary paresis and the parasympathetic lesion were marked, sensitivity was slight or absent.

The Site of the Lesion.—The lesion in the Holmes-Adie syndrome has been variously attributed to the following sites: (1) Proprioceptive fibres from the iris (Langworthy and Ortega, 1943); (2) the hypothalamus (Kennedy and others, 1938); (3) supranuclear ocular fibres (Lowenstein and Friedman, 1942). However, no lesion outside the efferent pathway of the light reflex could explain the loss of the direct reaction to light in a unilateral tonic pupil, with preservation of the indirect reaction in the normal pupil. The lesion must therefore be somewhere in the efferent pathway.

The apparent paradox of paresis and tonic reaction occurring in the same pupil can be explained by reference to the work of Cannon and Rosenblueth (1949) on the supersensitivity of denervated structures. Their law states that when a chain of neurons is severed, there results, after an interval, a supersensitivity of the distal elements and effectors to the action of nerve impulses, and to certain chemical

agents either injected parenterally or applied locally. Shen and Cannon (1936) performed a unilateral excision of the ciliary ganglion in the cat, and demonstrated that, after an interval of a few days, a locally instilled solution of acetyl choline caused a maximal contraction of the iris. This response of the iris to acetyl choline after a parasympathetic lesion is analogous to the sensitivity of sympathectomized structures to adrenaline. Although the practical importance of this phenomenon after surgical procedures in man has been exaggerated, as pointed out by Learmonth (1950), its occurrence during disease processes has not received the attention it deserves. It would certainly account for the pupillary abnormalities in the Holmes-Adie syndrome.

In the first place, it would explain why the iris becomes sensitive to cholinergic drugs. There are two possible ways in which this sensitivity develops: a deficient formation of cholinesterase may impair the removal of acetyl choline, or the effector cells of the sphincter pupillae may react to the drug in an exaggerated fashion. Both mechanisms probably operate, but the latter is the more important in view of the overaction to drugs such as pilocarpine, which are unaffected by cholinesterase.

Secondly, a comparison may be made with the Philipeaux-Vulpian phenomenon in which, as a result of stimulating the chorda tympani, a contraction of the tongue is obtained some days after the hypoglossal nerve has been sectioned. This pseudo-motor effect is thought to be the result of a diffusion of acetyl choline from the stimulated autonomic nerve endings to the denervated and sensitized striated muscle fibres (Cannon and Rosenblueth, 1949). The contraction is often slow and excessive—in fact, very much like that found in the tonic pupil. There acetyl choline presumably diffuses from intact parasympathetic nerve endings to denervated and sensitized smooth muscle fibres of the pupillary sphincter. This explanation is also offered by Scheie (1940) who thinks that all these pupils are hypersensitive to the cholinergic drug he used, namely, " mecholyl ". Supersensitivity is not invariably found, however, and it decreases when the parasympathetic lesion increases. It is precisely in such pupils that the tonic reaction is absent or slight, probably because little or no acetyl choline is liberated. Hence these features are absent in cases with ophthalmoplegia interna, a not uncommon manifestation of the Holmes-Adie syndrome.

In conclusion, the presence of pupillary paresis, with accompanying hypersensitivity to cholinergic drugs, places the site of the disturbance along the parasympathetic pathway between the third nerve nucleus and the short ciliary nerves. Whether the pre- or the post-ganglionic nerves are primarily affected remains uncertain, but there is some evidence in favour of the latter. In lesions of the sympathetic nervous system, sensitivity is usually more marked after post-ganglionic than after pre-ganglionic denervation, but Keil and Root (1942) point out that with parasympathetic denervation of the cat's iris the two different sections are often equal in their effect. On the other hand, there are records of tonic pupils developing after injuries or tumours established as affecting the ciliary ganglion or short ciliary nerves (Axenfeld, 1906; Ohm, 1907; Cords, 1930; Garcin and Kipfer, 1936). Moreover, the constant irregularity of the pupil points to a selective segmental denervation, such as would be produced by patchy involvement of the short ciliary nerves. The ciliary ganglion is thought to be the site of the lesion by Magitot (1911), Scheie (1940), and Leathart (1942), whereas Behr (1921) and Adie (1932) suggest that the third nerve nucleus is implicated. This concept of sensitization to the effect of acetyl choline is quite distinct from Saenger's theory of a primary muscular abnormality independent of denervation (1902), for which there is no supporting evidence.

Classification of the Abnormal Pupil.—Many variants of the tonic pupil are recognized in clinical practice, and for the purposes of classification some unifying theme is needed. Adie recognizes "atypical" pupils, the term being used to include pupils which are fixed. This is criticized by McKinney and Frocht (1940) on the grounds that confusion may arise with other causes of ophthalmoplegia interna, including syphilis. Nevertheless, most authors accept these divergencies from the classical appearances, and Graveson divides his cases into those with " fixed " and those with " ordinary " types of pupil.

It must be accepted, moreover, that Holmes-Adie pupils are seldom identical, and that there are innumerable variations between the forms which I shall term " paralytic " and truly " tonic ". The variations depend on the severity of the lesion and on its duration, since the degree of paralysis or sensitization of the sphincter muscle of the iris is determined by these two factors. When the parasympathetic fibres have been recently and completely destroyed, the pupil fails to constrict on convergence, does not become miotic after stellate ganglion block, and is not supersensitive to cholinergic drugs. The tonic pupil, on the other hand, is found some time after a lesser degree of parasympathetic damage; the pupil responds more fully to convergence and

sympathetic denervation, and a slow contraction and relaxation are evident, together with an enhanced response to the parasympathomimetic drugs. It must be pointed out that the enlargement of the pupil, commonly encountered, does not necessarily indicate that the defect is mainly one of paralysis. Two of the largest pupils in this series (Cases 2L and 11) were remarkably tonic in their response, and became exceedingly small on stellate ganglion block, indicating that their size was maintained by sympathetic activity. It is interesting to note that in one patient (Case 2) both pupils were dilated, the right being " paralytic " in type and the left " tonic ".

Finally, the evolution of the disturbance can be understood in terms of either a development of sensitivity or a recurrence of paralysis. The first manifestation of the disease, and it must be called a disease, is usually the appearance of a " paralytic " type of pupil. In time, if the damage has been only partial, some tonicity appears. Relapse may occur after an interval of months or years, but this is usually in the other eye. Adie does state that the tonic reaction may subsequently disappear, but this has not been observed by others (Alajouanine and Morax, 1938). Theoretically, there is no reason why such a recrudescence should not take place on the same side. The associated defect of accommodation has the same natural history: paralysis, with recession of the near point, is followed by delayed contraction of the ciliary muscle and slowing of accommodation. When the ciliary muscle is affected, its involvement is usually simultaneous with that of the sphincter pupillae, but is of a different degree. The tendon reflexes may be involved at any stage of the clinical course.

Summary

Fourteen cases of the Holmes-Adie syndrome are reviewed, and an attempt is made to clarify the pathogenesis of the pupillary disturbance by studying the effect of stellate ganglion block and of the conjunctival instillation of drugs. The main defect is one of parasympathetic denervation, the sympathetic remaining intact. The tonic contraction and delayed relaxation indicate supersensitization of the denervated sphincter pupillae to acetyl choline liberated by intact parasympathetic fibres.

The lesion is in the efferent parasympathetic pathway, and is probably post-ganglionic.

Depending on the respective degree of paralysis and supersensitization, wide clinical variations may be met, but two broad types are recognized—" paralytic " and " tonic ". The natural history of the disease may be one of repeated episodes affecting the pupils, the function of accommodation, and the tendon reflexes in turn.

I wish to thank Dr. John Marshall for encouragement with this work, and Drs. J. B. Stanton and E. B. French, Prof. Sir Stanley Davidson, and Prof. J. W. Crofton for granting me access to patients under their care.

References

Adie, W. J. (1932). *Brain*, **55**, 98.
Alajouanine, T., and Morax, P. V. (1938). *Ann. Oculist (Paris)*, **175**, 205.
Axenfeld, T. (1906). *Dtsch. med. Wschr.*, **32**, 663.
—— (1919). *Klin. Mbl. Augenheilk.*, **62**, 59.
Barré, J. A., and Klein, M. (1934). *Rev. neurol. (Paris)*, **1**, 590.
Behr, C. (1921). *Klin. Mbl. Augenheilk.*, **66**, 770.
Cannon, W. B., and Rosenblueth, A. (1949). *The Supersensitivity of Denervated Structures*. Macmillan, New York.
Cords, R. (1930). *Zbl. ges. Neurol. Psychiat.*, **55**, 701.
Garcin, R., and Kipfer, M. (1936). *Rev. neurol. (Paris)*, **65**, 128.
Graveson, G. S. (1949). *Journal of Neurology, Neurosurgery and Psychiatry*, **12**, 219.
Holmes, G. (1931). *Trans. ophthal. Soc. U.K.*, **51**, 209.
Jaffe, N. S. (1950). *Arch. Ophthal. (Chicago)*, **44**, 710.
Keil, F. C., and Root, W. S. (1942). *Amer. J. Physiol.*, **136**, 173.
Kennedy, F., Wortis, H., Reichard, J. D., and Fair, B. B. (1938). *Arch. Ophthal. (Chicago)*, **19**, 68.
Langworthy, O. R., and Ortega, L. (1943). *Medicine (Baltimore)*, **22**, 287.
Learmonth, J. R. (1950). *Lancet*, **2**, 505.
Leathart, P. W. (1942). *Brit. J. Ophthal.*, **26**, 60.
Lowenstein, O., and Friedman, E. D. (1942). *Arch. Ophthal. (Chicago)*, **28**, 1042.
McKinney, J. M., and Frocht, M. (1940). *Amer. J. med. Sci.*, **199**, 546.
Magitot, A. (1911). *Ann. Oculist (Paris)*, **145**, 258.
Moore, D. C. (1954). *Stellate Ganglion Block*. Charles C. Thomas, Springfield, Illinois.
Moore, R. F. (1931). *Trans. Ophthal. Soc. U.K.*, **51**, 203.
Ohm, J. (1907). *Zbl. prakt. Augenheilk.*, **31**, 193.
Reitsch, W. (1925). *Klin. Mbl. Augenheilk.*, **74**, 159.
Rothmann, M. (1903). *Neurol. Zbl.*, **22**, 242.
Saenger, A. (1902). *Ibid.*, **21**, 837 and 1137.
Scheie, H. G. (1940). *Arch. Ophthal. (Chicago)*, **24**, 225.
Shen, S. C., and Cannon, W. B. (1936). *Chin. J. Physiol.*, **10**, 359.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 297

SENSORY DEFICITS IN VISUAL AGNOSIA

BY

GEORGE ETTLINGER

*From the Psychological Laboratory, Institute of Neurology, Queen Square, London**

In recent years, Bay (1950, 1953) has repeatedly claimed that the so-called " higher " perceptual disorders are secondary to sensory impairment, to general intellectual loss, to language disturbance, or to a combination of these three factors. He denies strongly that agnosia in its classical sense of a circumscribed defect of recognition, specific to a single sense modality, in reality exists. Bay maintains that abnormal alterations in visual function (*pathologischer Funktionswandel*) may be present in cases conventionally held to display symptoms of agnosia and may play an important role in the genesis of this disorder. Although these sensory deficits may escape detection on routine examination of the visual fields, it is argued that they are measurable by means of a special test of local adaptation. This test has been fully described by Bay (1950, 1953). His results indicate first, that alterations in adaptation rate are prominent in most patients with clinical signs of agnosia; and secondly that such visual deficits may occur in perimetrically normal areas of the visual field. In general, Bay reports that significant alterations in visual efficiency are present in all cases of " agnosia " in which there is neither disorder of language nor significant global deterioration.

These contentions have been critically examined at a symposium of German neurologists held in 1951. The consensus of opinion cannot be said to favour Bay's interpretation. Thus it was argued by both Jung (1951) and Scheller (1951) that visual impairment together with non-specific intellectual loss could hardly explain the diversity of visual-agnosic syndromes and their relative specificity in terms of content (object agnosia, alexia, spatial agnosia, etc.). Faust (1951, 1955) has drawn a distinction between genuine and " pseudo-agnosic " symptoms; only the latter, he believes, are to be explained in terms of sensory loss in the manner proposed by Bay. It is also noteworthy that Russell (1951) has reported accelerated visual adaptation in the absence of visual agnosia; and Jaffe (1955) has more recently described accelerated tactile adaptation without astereognosis. It would therefore appear that although sensory defects of the kind proposed by Bay may well occur in many cases of brain lesion, their relation to the classical agnosias is decidedly conjectural.

It should also be pointed out that there are certain methodological defects in the test procedure as reported by Bay (1953). In the first place, the effects of unilateral visual inattention (extinction) do not appear to have been given adequate consideration despite Bay's use of the condition of double simultaneous stimulation. In the second place, Bay's method of assessing the degree of adaptation defect in a particular patient by subtracting the value given from the mean value for an appropriate control group is far from satisfactory. It will readily be seen that this method would permit some " abnormality " to be recorded in about 50% of a healthy population. In the third place, Bay's method, which places stress on chromatic adaptation, is open to the objection that disturbances in colour recognition are commonly unrelated to other varieties of agnosia.

Despite these and other objections to Bay's methods, his views concerning agnosia have gained some measure of acceptance (cf. Critchley, 1953). Apart from purely theoretical issues, however, careful examination of more elementary visual processes in the manner suggested by Bay would appear a most valuable precaution in the analysis of cases presenting " higher " visual disabilities. An investigation has therefore been undertaken to assess the extent and significance of visual deficit in a series of 30 cases of brain lesion. These comprise (*a*) cases lacking both visual field defects (as conventionally ascertained) and signs of perceptual disorder (12 cases); (*b*) cases with field defects but without perceptual disorder (10 cases); (*c*) cases with field defects and various types of perceptual disorder (" agnosia ") (eight cases). These patients were tested on a variety of visual discrimination tasks using systematic psychophysical procedures, and the results evaluated with reference to the thresholds given by a large control group of healthy

* This report describes part of work which has been approved by London University for the award of the Ph.D. degree.

subjects. It is hoped first, to determine the incidence and magnitude of visual deficits in cases of cerebral lesion; and secondly, to assess their possible significance in relation to the " higher " disorders of visual perception.

Apparatus

An apparatus was constructed to enable discrimination on a variety of visual tests to be assessed quantitatively at representative points in the visual field. This apparatus allows all variables not directly related to the differences between the tests, *e.g.*, background luminance, to be held constant.

An hemisphere made of plaster and of 1 m. radius is set vertically in a room which can be fully screened from daylight (Fig. 1). The smooth inside of the hemisphere is coated with special matt white diffusing paint according to a formula developed by the G.E.C. Ltd. to reflect light of all wave lengths approximately equally. A large corrected field lens is mounted behind a circular aperture of 6·3 cm. diameter let into the centre of the interior surface of the hemisphere. The interior is illuminated by two 4 ft. 40 w. " natural Osram " fluorescent tubes suspended vertically one to each side, at about $2\frac{1}{2}$ ft. from the rim. These tubes are supplied with 230 v. A.C. from a constant voltage transformer. The luminance of the central part of the hemisphere is always maintained at a level of 34·7 ft. L. $\pm$ 5%.

Test stimuli are presented from the centre of the surface of the hemisphere, *i.e.*, through the lens or from close to it. The subject can be instructed to fixate on either the stimuli themselves (to test central vision) or on any point of the interior surface of the hemisphere which may be indicated by fixing a small black mark at the required position. For standard testing, small 2 v. torch bulbs are imbedded into the plaster at 5°, 15°, and 35° along the four diagonals running up and to the left, down and to the left, down and to the right, and up and to the right from the centre of the field lens, and serve as fixation lights. These bulbs are only faintly illuminated when required, and only their filaments can then be seen to glow through 2 mm. apertures in the white paint. Similarly, neon " indicator " lamps are positioned, one each, at 2·5° from the centre of the field lens along each of the four diagonals, so that their top ends lie flush with the interior surface of the hemisphere. Pieces of diffusing paper are attached to the top ends of the neon bulbs and have small black crosses painted at their centres.

A specially designed head rest is mounted on a supporting platform in such a way that the whole of it can rotate about a vertical axis, and part of it (including the chin and brow rests) can rotate about a horizontal axis. The point of intersection of these axes is also the exact centre of the hemisphere, *i.e.*, at 1 m. from every point of the interior surface. Either one of the subject's eyes can without difficulty be accurately positioned at this point, since the height of his chair and the deviation of the chin and brow rests from the horizontal and vertical axes are all adjustable. The head rest can be turned and tilted (without the eye shifting from its required position in relation to the field lens) so that the forehead is square to the optical axis for all fixation points. This eliminates that component of ocular fatigue which arises when fixation is maintained by ocular deviations away from the central position of the eyes in the head.

To ensure that fixation is maintained on the required point, a small hole ($\frac{1}{8}$ in. diameter) is drilled through the plaster of the hemisphere at eye level from the ground and at 20° from the centre of the interior surface. Through this the subject's fixation can be observed. A standard procedure is adopted for the different tests with regard to the few instances when a shift from the fixation point is observed, but in practice it is found that if the subjects are promptly checked and warned not to " cheat ", steady fixation is maintained after the first test or so.

An optical system, the position of which relative to the hemisphere is roughly indicated (not to scale) in Fig. 1, permits various light stimuli to be presented through the field lens. At the same time it fills the field lens, which is seen in Maxwellian view (cf. Leibowitz, 1954), with light. The details of the optical system are illustrated in Fig. 2.

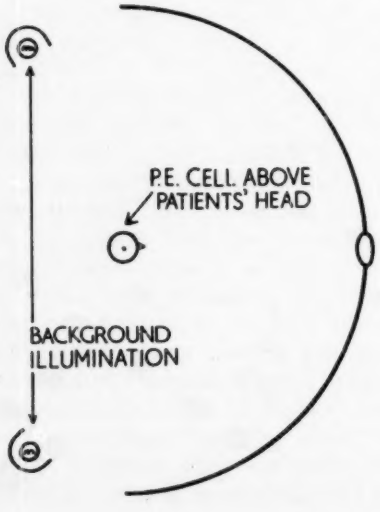


FIG. 1.—Hemisphere and light source.

Two channels of light are taken from one source, a vertical 2 ft. 40 w. " natural Osram " fluorescent tube, and are recombined in a mixing cube. The light of the background channel merely passes through wedge filters which permit an exact subjective match to be made between the brightness of the field lens and of the interior of the hemisphere. Cuts of

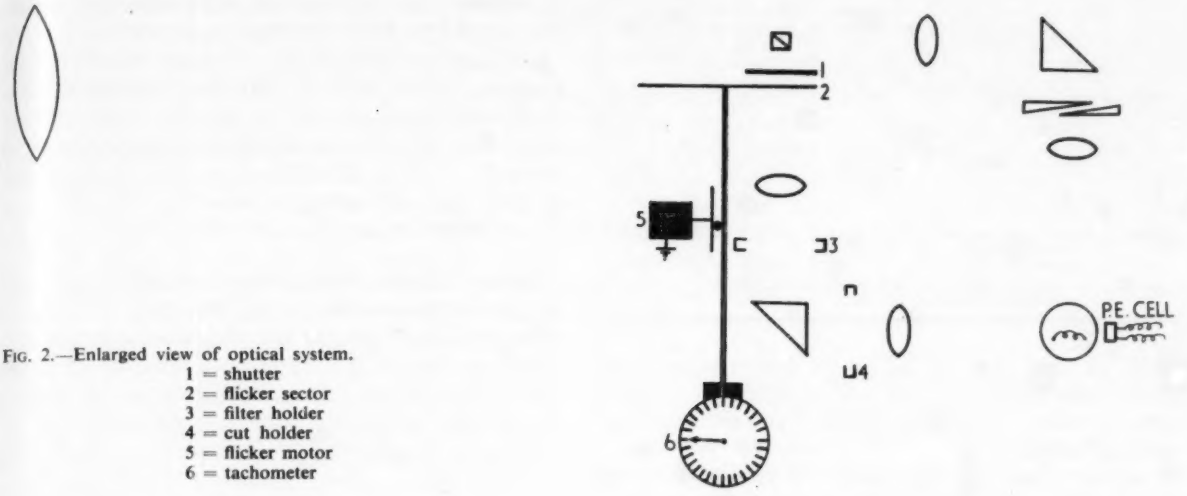


FIG. 2.—Enlarged view of optical system.
1 = shutter
2 = flicker sector
3 = filter holder
4 = cut holder
5 = flicker motor
6 = tachometer

any desired shape or size, and filters of any kind can be inserted into the cut and filter holders positioned along the axis of the stimulus channel. The images of the cuts are seen in the plane of the interior surface of the hemisphere. An electrically operated shutter can be set for stimulus exposures of 1 sec. or longer as required.

In order to minimize the 100 cycle component in the output of the 2 ft. 40 w. fluorescent source, the tube is supplied through a rectifier unit and the output voltage smoothed by means of an electrolytic capacitor. The associated control gear of the lamp unit is retained with the addition of a variable resistor and reversing switch. The residual ripple constitutes 8·5% of the total light output of this source which has a luminance of 3,162 ft. L. ± 2%. The range variation at one session is normally ± 0·5%, and control of the source luminance is achieved by use of the variable resistor on the output side of the constant voltage supply to regulate the current passed to the tube. Blackening of the tube is prevented by frequently reversing the direction of the current.

Visual Discrimination Tests and Control Performance

The particular tests used in this study comprised brightness discrimination (B.D.), flicker fusion (F.F.), acuity for small objects (Ac.), local adaptation (L.A.), tachistoscopic acuity (T.A.), and apparent movement perception (A.M.). A control group of 48 normal individuals, drawn from the staff of the National Hospital, was used in standardizing the tests. Its composition is fully described elsewhere (Ettlinger, 1955). The mean age of this group was 34·7 years, with a range of 17 to 61 years. Each control subject was tested with both eyes separately and on all the tests, each patient with one eye only. Three points along the diagonal meridian of each quadrant (2·5°, 15°, and 35° for B.D., F.F., and L.A.; 5°, 15°, and 35° for Ac., T.A., and A.M.) were selected for standard testing, with the addition of central vision for B.D., F.F., and A.M. The order of testing eyes, quadrants, and points within quadrants was systematically varied for both control subjects and patients to balance practice effects. The sequence of the administration of the different tests was randomly varied. The interval of time between test sessions varied for all subjects from 24 hours to a few weeks. A standard rest period of two minutes is allowed in between the testing of successive quadrants.

In presenting the results for the control group, the findings for the right and left eyes are combined, as are those for the four quadrants tested. This procedure has been adopted because no significant differences were found between results analysed separately for eyes and quadrants, *i.e.*, between upper and lower, right and left, or nasal and temporal quadrants. The thresholds obtained for 48 control subjects using two eyes on each test are also combined because no systematic relationship between performance with the first and second eye could be detected for a random sample of eight of the control group on any test.

The background luminance of the hemisphere and field lens is held constant at 34·7 ft. L., but the dimensions of the various test objects presented in the different discrimination tasks are summarized for each test separately below.

The procedure and control results may now be reported for each test.

Brightness Discrimination Tests.—The just-noticeable difference in brightness between the test object and the background is determined by the method of serial groups. The luminance of the test object can be decreased from the standard incremental value (measured against an unfilled

Test	Nature of Test Object	Angular Size of Test Object	Incremental Luminance of Test Object	Duration of Exposure
B.D.	Central circular disc	1·5°	Variable	1·5 sec.
F.F.	Central circular disc	1·5°	199·5 ft. L. (light phase)	1·5 sec.
Ac.	Central modified Landolt rings	Variable	199·5 ft. L.	1·5 sec.
L.A.	Central circular disc	1·5°	199·5 ft. L.	—
T.A.	2 pairs of neon lamps, round field lens	Each lamp 53 min.	58·9 ft. L.	Variable
A.M.	4 neon lamps round field lens	Each lamp 53 min.	58·9 ft. L.	5 sec.

field lens) of 199·5 ft. L. by the insertion into the stimulus channel of one of a series of neutral density filters. These are graded in steps of 0·25 log. units of density.

At each level of luminance the subject is given 10 " presentations ", *i.e.*, the shutter is operated 10 times, but in only five of these, at random, is the disc of light actually exposed. The luminance level of the last group of the series (from easy to difficult) in which eight out of 10 responses are correct is recorded as the threshold value. A response " yes " to no exposure is counted incorrect just as is " no " to a faint presentation. No account is taken of errors in groups containing eight correct responses or of correct answers in unsuccessful groups. A period of one to two seconds is allowed between successive presentations and some provisions are made for practice at discrimination on the first quadrant of each test session.

The results at brightness discrimination in central vision and at angular separations of 2·5°, 15°, and 35° from the visual axis for the middle 80% of the control group are presented in Table I. Ten per cent of all the values obtained have been excluded from each extreme end of this and every other distribution of control data. N refers to the total number of control values from which the " normal " range of any category of response is derived. As explained above the results for right and left eyes and different quadrants have been combined. In addition, the normal ranges of performance were determined for the following categories of response (" normal " in this context represents the results for the middle 80% of a control group):—

(1) Sum of thresholds at three points in one quadrant (N = 383); (2) difference between sums of thresholds at three points in the right and left quadrants (combining upper and lower quadrants when N = 191); (3) difference between thresholds at right and left points, comparing 2·5°, 15°, and 35° each separately (N = 192, 192, 191).

Flicker Fusion Tests.—Two ascending and two descending thresholds are obtained using the method of minimal changes, for the phenomenal fusion of a flickering disc of light. Each presentation of flicker has a duration of 1·5 sec. with intervals of one to two seconds in between successive presentations.

A metal disc having four sectors is driven by a constant speed motor through a " ball and disc " type of gear box and is mounted as illustrated in Fig. 2 so that it interrupts the stimulus light beam close to its narrowest cross-section. The blades of this disc give a 1 : 1 light-dark ratio, where the dark phase is the background luminance of the field lens. A Smith's hand tachometer (Model A.T.H.7) is locked to the sector shaft and thus gives a direct reading of its rate of rotation.

The normal ranges of the mean c.f.f.s in central vision and in the peripheral field are presented in Table I. In addition, the normal ranges of the deviations of the individual flicker thresholds from their mean at any point were ascertained. This measure reflects the normal variability of performance at flicker fusion at one position in the visual field. The normal ranges for further categories of response were also determined, as for brightness discrimination, except that no sums of thresholds at three points in one quadrant were taken. This additional category of response has been omitted because change of fusion frequency in relation to the eccentricity of the test object was not uniformly in the same direction for all subjects as is reported elsewhere (Ettlinger, 1956).

Acuity for Small Objects Test.—In order to determine the acuity for small objects progressively

TABLE I

NORMAL (80%) RANGES OF PERFORMANCE BY CONTROL GROUP ON TESTS OF BRIGHTNESS DISCRIMINATION FLICKER FUSION, ACUITY FOR SMALL OBJECTS, LOCAL ADAPTATION AND TACHISTOSCOPIC ACUITY

	N*	B.D. (Δ I/I, fractional differences)	F.F. (Mean C.f.f.s in c.p.s.)	Ac. (Angular Sizes in Min. and Sec. of Arc)	L.A. (Middle Times in Sec.)	T.A. (Duration of Flashes in msec.)
Central vision	96	0·0057—0·018	72·5—42·5			
2·5°	384	0·0102—0·032	60·5—40·0		120+—11	
5°	384			1′ 4″— 2′ 9″		1·5—5·4
15°	384	0·032—0·057	63·5—35·5	8′ 35″—17′ 10″	30— 5	5·4—14·5
35°	383	0·057—0·181	61·5—32·5	34′ 20″—137′ 20″	20— 4	14·5—80·0

* N refers to the number of thresholds on which any range is based.

smaller "modified" Landolt rings are presented by the method of serial groups from the centre of the field lens. The gap in the ring faces twice in each direction (in random order) in each group, and testing is continued until the direction of the gap cannot be correctly discriminated in six out of the eight trials allowed for any one size of gap.

The modified Landolt rings are prepared from thin copper foil and are then attached to glass slides. Since the image of any cut has dimensions about three times greater than those of the cut itself owing to the characteristics of the optical system, modified Landolt rings were developed in which the angular size of the rings is maintained constant (at 2·3° outer, 1·5° inner diameter) for variations in the magnitude of the gap ranging from 1 min. 4 sec. to 68 min. 40 sec. Unfortunately certain disadvantages are inherent in this design.

Small differently coloured marks can be attached to the surface of the hemisphere close to the lens in the four directions, *e.g.*, red to the left, blue to the right, etc., to assist those patients who have right/left disorientation.

The normal ranges of performance are given in Table I. The normal ranges for additional categories of response were also determined, as for brightness discrimination.

Local Adaptation Test.—In the test of local adaptation three values for the time of subjective disappearance of a disc of light after its exposure are recorded for each position of the visual field tested. Taking one quadrant at a time, the positions along it are tested once each in rotation and then for the second and third times again in rotation.

The subject is given standard instructions part of which read: "If the bright central disc appears to you to fade from view into the background I want you to press this key here. If the disc does not appear to fade from view into the background within a certain time, I shall switch it off. You should avoid blinking more frequently than is necessary, and you should *not* press the key if the disc has disappeared from view only during a blink. On the other hand, you *should* press the key if the bright central disc has appeared to fade from view into the background *even for a moment only* and then has reappeared." An electrical clock is started synchronously with the exposure of the disc and stopped by the subject when he presses the key.

The maximum exposure time is 120 sec., and a response category of 120+ is recorded if the subject has failed to press the key within this interval. In order to ensure that the prolonged local adaptation times manifested by some patients are not the result of inadequate comprehension of instructions but are genuinely visual phenomena, the disc can be silently obscured. Such checks are only made after the disc has been exposed for 120 sec., and the threshold value is discounted if the subject has failed to press the key within 5 sec. of the obscuration.

In computing the normal ranges of performance (Table I) account has been taken of only the middle one of the three values recorded at any position in the field of vision. The normal ranges of variability at local adaptation were ascertained by including the deviations of the two remaining readings from the middle time at each position in one frequency distribution. In addition, the normal ranges for other categories of response were also determined, as for brightness discrimination.

Tachistoscopic Acuity Test.—Tachistoscopic acuity is evaluated by flashing one of two pairs of neon lamps on for progressively shorter durations until the stimulus pair cannot be identified correctly in eight out of the 10 trials allowed for any one duration of flash.

The 240 v. neon indicator lamps positioned at 2·5° along the four diagonal meridians from the centre of the field lens are employed. They are wired for this test in pairs, the bulbs at the diagonally opposite corners of the square being connected together. Each pair is presented five times (in random order) in each group of 10 trials. Their light has an orange red appearance.

The neon tube circuit is completed by means of a pair of high speed relay contacts, and the current pulse for the operating coil of this relay is drawn from a capacitor charged to a suitable potential. Variation of the flash duration is achieved by selecting the appropriate one of five capacitors giving times ranging from 1·5 to 80 msec. In the course of the investigation all flash durations have varied by approximately ±5%, and a further disadvantage relates to the relatively large angular size of the test pairs.

The normal ranges of performance are shown in Table I. The normal ranges for additional categories of response were also determined, as for brightness discrimination.

Apparent Movement Perception Test.—The four neon lamps at 2·5° from the centre of the field lens are illuminated in anti-clockwise rotation in order to test apparent movement perception. The standard parameters of stimulation, *i.e.*, exposures lasting 160 msec. and intervals between exposures of 40 msec., are such as have been found to give optimal perception of apparent movement with a small pilot group. Only one presentation, lasting 5 sec., is made under the standard conditions at each position in the visual field, and the subject is then

immediately questioned about his experience. Answers are sought according to five categories of experience, but leading questions are avoided and the subject is not pressed to answer if he is uncertain.

The four neon lamps are supplied through contacts on an electrically driven cam operated switch, and variation of the motor speed will adjust the period of the complete stimulus cycle (from 0·6 to 2·0 sec.). On the other hand, movement of the wedge-shaped operating cam in relation to the switch contacts allows the on-off ratio of the lamps to be altered (from 0·46 to 1·16, *i.e.*, so that successive flashes may overlap).

The relative frequencies of two out of the five categories of response for the control group are presented in Table II, where N refers to the number of positive responses on which any percentage is based.

TABLE II

CONTROL RESULTS ON TEST OF APPARENT MOVEMENT PERCEPTION (% INCIDENCE OF ALTERNATIVE RESPONSES)

	N	Movement	No Movement		
Central	94	91·5	8·5		
5°	384	95·3	4·7		
15°	384	99·7	0·3		
35°	383	94·0	6·0		
	N	Square Shape	Circle	Others	No Shape
Central	86	79·1	18·6	0·0	2·3
5°	367	62·1	30·8	4·1	3·0
15°	376	22·6	66·2	9·1	2·1
35°	355	9·9	56·1	8·5	25·5

The response category of " movement " includes any impression of movement, whatsoever its nature. The most common alternative report was to the effect that the lights merely flashed on and off successively. When a response of " no movement " was given, the temporal parameters of stimulation were varied over the ranges described above. In about one half of these cases the perception of movement could then be evoked, but no systematic trend became evident implicating either shorter or longer durations of illumination or of intervals between illuminations as more effective in promoting the perception of movement than the standard conditions. Mere repetition of presentations to one retinal position may, therefore, exert a facilitating effect, independently, within certain limits, of the temporal parameters of stimulation. At all positions some responses of " no shape " probably reflect uncertainty rather than a positive absence of perceived shape.

In about 10% of all responses a phenomenal change in the display occurred during the 5 sec. presentation. In such cases only the predominating appearance was included in the results analysed. A number of subjects also spontaneously reported a diminution in the apparent size of the display at 35° by comparison with its appearance at 15° and 5°. Information concerning the other categories of response is given by Ettlinger (1955).

Test-Retest Correlations

The rank test-retest correlations were calculated on all the tests excepting apparent movement perception for a group of eight control subjects selected at random. Applying one-tailed tests of significance and adopting the conventional 5% level of confidence, these test-retest correlations proved significant in every instance with the exception of acuity for small objects.

Selection of Cases

A group of 30 patients has been studied. Of these only one (Case 23) was selected for the presence of visual perceptual disorder and was referred by Dr. C. A. Pallis for examination (Pallis, 1955). The remainder comprised 22 cases of cerebral disease and five cases of brain injury. Two cases presented visual deficits associated with optic atrophy. With one exception (Case 30)* no case with severe intellectual deterioration was included, although there were minor degrees of impairment in several. These were not, however, thought to be sufficient to disturb cooperation on the tests.

The cases were divided into three groups on the basis of the presence of visual field defects and/or evidence of higher perceptual disorder. Group A comprises 12 cases lacking both field defects and evidence of perceptual disorder; group B comprises 10 cases with various types of field defect but without evidence of perceptual loss other than that directly attributable to the field defects; group C comprises eight cases in which both field defects and various types of higher perceptual disorder were in evidence. The salient data in the individual cases in each group are summarized in Tables III, IV, and V.

No pupillary abnormalities were present in the eye tested of any patient apart from Case 17, and disturbance of eye movements during fixation was observed only in Case 24. Reasonable allowance for various other clinical features such as dysphasia (Cases 1, 2, and 25) and right/left disorientation was made by slight alterations of procedure, but tests were abandoned in all instances in preference to the

* Case 30 has been included because he demonstrates that sensory thresholds can be determined for patients of extremely defective intelligence.

introduction of any significant departure from the standard procedures. Results of clinical tests of central visual acuity were available in every case and are given in detail elsewhere (Ettlinger, 1955). No exceptional values were reported.

Procedure and Treatment of Results

In general the patient's more " effective " eye (by reference to clinical tests of acuity or perimetry) was selected for testing, but where vision seemed to be essentially the same in the two eyes the choice was made by a random procedure. An exception to this rule was made in one case of optic atrophy (Case 19) when the eye with least effective vision was chosen for tests of both perception and sensory efficiency.

Although thresholds were obtained for some patients at positions in the visual field additional to the standard points used with the control group, *e.g.*, for the vertical and horizontal meridians, these data have been neglected in computing two overall measures of visual sensory performance for each patient, the " efficiency index " and the " variability index ". Details of the method of calculating these indices are given by Ettlinger (1955). In outline, however, the patient's performance is compared with the appropriate normal range, taking the threshold obtained at each of the standard positions in the visual field separately, as also certain additional categories of response.*

If performance at any point or according to any additional category of response falls within the normal range it is allotted a " transformed " score of zero; if it falls outside the normal range in the direction of less efficient performance or of greater variability between successive discriminations, it is allotted a transformed score of -1; if it falls outside the normal range in the direction of more efficient performance or of less variability between successive discriminations it is allotted a transformed score of $+1$. The algebraic sums of these transformed scores, taking scores relating to efficiency and variability separately, are found either for one test at a time or for all tests in combination.†

In order to eliminate the positive or negative signs of the algebraic sums of transformed scores, and to allow for the varying numbers of transformed scores on which these sums may be based, a mathematical conversion to indices is effected. Thus a positive algebraic sum of transformed scores is added to the total of transformed scores on which it is based and the resulting value is expressed as a ratio of this total, times 100; if the sum of transformed scores is negative, it is subtracted from the total number of transformed scores on which it is based, and the difference is expressed as a ratio of this total, times 100. An index of 100 then represents the level of performance relating to the middle 80% of the control data, and values greater or smaller than 100 are related to more or less efficient or consistent levels of performance respectively. However, owing to a scoring bias which affects all the patients' results equally, efficiency indices greater than 100 in value are slightly less probable than values below 100.*

In computing efficiency indices, a transformed score of -1 is allotted both for performance relating to a totally blind area of the visual field and for a threshold determination falling just outside the normal range of performance. Account is, however, taken of the difference between these two kinds of result in charting each patient's performance at different sites in the visual field with a graphical technique described elsewhere (Ettlinger, 1955).

Results

The efficiency indices on the individual tests and on all the tests in combination for the 30 patients are given in Tables III, IV, and V. It will be seen from Table III that the mean overall efficiency index for the 12 cases with perimetrically normal fields is found to be 82. This signifies that there is some overall impairment of sensory efficiency relative to the standard of the control subjects despite the lack of field defects as conventionally determined. It is improbable that the sensory impairment of patients in Group A is related to the slightly greater mean age (38·2 yr.) in this group than in the control group. The effect of the scoring bias may also be discounted since the mean efficiency index for 11 of the 12 patients tested at brightness discrimination is still only 89, although the bias is negligible in this test. These scores on brightness discrimination (which may be shown to be significantly lower than control values at the 1% level

* These have been mentioned in the description of the sensory tests. There are four scores in each test (excluding flicker fusion and apparent movement) for the sums of three thresholds in one quadrant. Comparisons between performance in the left and right half-fields are always allotted two scores, whether quadrants or individual sites are contrasted. In the test of apparent movement perception only " movement " and " shape " responses are compared with control data. One measure of variability is taken for each threshold, where applicable, for computing variability indices.

† One " transformed " score is also allotted for performance on a test of real movement perception in central vision, and this is included in the algebraic sums of " transformed " scores for all the tests in combination.

* Owing to the significant excess of positive transformed scores at L.A. (see below), algebraic sums of transformed scores derived by a different method are incorporated into the overall efficiency indices. Thus both positive and negative transformed scores are treated as negative, but the negative total is reduced by a constant factor to allow for the 20% expectation of both positive and negative transformed scores.

TABLE III

EFFICIENCY INDICES FOR INDIVIDUAL TESTS AND FOR TESTS IN COMBINATION IN CASES WITHOUT FIELD DEFECTS OR PERCEPTUAL LOSS (GROUP A)

Case	Sex	Age	Diagnosis	Efficiency Indices (normal = 100)						
				B.D.	F.F.	Ac.	L.A.	T.A.	A.M.	Overall
1	M	33	Left temporo-parietal subdural haematoma	100 (19)*	69 (15)	95 (19)	111 (18)	89 (18)	100 (26)	93 (116)
2	M	52	Left temporo-parietal lesion of unknown aetiology	95 (19)	107 (15)	89 (19)	78 (18)	67 (18)	75 (23)	85 (113)
3	M	19	Left temporal lobe E.E.G. focus; excision	84 (19)	91 (15)	94 (18)	111 (18)	122 (18)	0 (13)	85 (101)
4	F	31	Right temporal lobectomy	74 (19)	38 (15)	79 (19)	139 (18)	44 (18)	84 (25)	68 (115)
5	M	57	Left fronto-parietal parasagittal G.S.W.	95 (19)	98 (15)	100 (18)	111 (18)	67 (18)	60 (20)	85 (109)
6	F	43	Left frontal angioma	79 (19)	25 (15)	72 (18)	167 (18)	50 (18)	92 (25)	65 (114)
7	F	37	Left fronto-parietal parasagittal glioma; partial excision	100 (19)	98 (15)	100 (19)	167 (18)	50 (18)	87 (23)	82 (113)
8	M (L-handed)	38	Left frontal lesion of unknown aetiology	95 (19)	47 (15)	89 (19)	106 (18)	111 (18)	100 (26)	92 (116)
9	M (L-handed)	35	Right mid-fronto-parietal G.S.W.	95 (19)	93 (15)	89 (19)	83 (18)	44 (18)	96 (26)	89 (116)
10	M	46	Right frontal glioma		96 (15)	111 (18)	156 (18)	100 (18)	85 (26)	90 (96)
11	M	45	Right frontal lesion of unknown aetiology; focal epilepsy	100 (19)	16 (15)	100 (19)	167 (18)	78 (18)	84 (25)	74 (114)
12	M (L-handed)	22	Severe contusional midbrain injury	58 (19)	20 (15)	100 (19)	100 (18)	40 (18)	84 (26)	72 (113)

* Values in brackets refer to the number of " transformed " scores on which any index is based.

TABLE IV

EFFICIENCY INDICES FOR INDIVIDUAL TESTS AND FOR ALL TESTS IN COMBINATION IN CASES WITH FIELD DEFECTS BUT WITHOUT PERCEPTUAL LOSS (GROUP B)

Case	Sex	Age	Diagnosis	Field Defects	Efficiency Indices (normal = 100)						
					B.D.	F.F.	Ac.	L.A.	T.A.	A.M.	Overall
13	M	27	Left occipito-parietal parasagittal G.S.W.	Partial R. homonymous hemianopia	26 (19)*	43 (15)	26 (19)	89 (18)	6 (18)	83 (24)	45 (113)
14	F	13	Right occipital lesion of unknown aetiology	Concentric constriction more marked to left	63 (19)	40 (51)	42 (19)	—	47 (18)	65 (23)	53 (113)
15	F	43	Right parieto-occipital neoplasm	L. homonymous hemianopia	42 (19)	14 (14)	37 (19)	50 ((18)	39 (18)	65 (20)	45 (108)
16	F	45	Right mid-parietal meningioma; excision	L. homonymous lower quadrantic defect	47 (19)	17 (15)	67 (18)	94 (18)	—	88 (25)	67 (96)
17	M	30	Right mid-fronto-parietal G.S.W.	L. homonymous lower quadrantic defect	61 (19)	67 (15)	58 (19)	75 (18)	17 (18)	92 (24)	66 (114)
18	M	26	Cerebral lesion of unknown aetiology; epilepsy	Inconstant defects	58 (19)	36 (15)	37 (19)	83 (18)	50 (18)	83 (23)	61 (113)
19	M	27	Suprasellar meningioma; right subtotal frontal lobectomy	Bitemporal constriction	21 (19)	13 (15)	47 (19)	167 (18)	17 (18)	50 (18)	35 (108)
20	M	61	Optic atrophy related to pituitary adenoma	Right eye blind, concentric constriction more marked to L. in L. eye	11 (19)	7 (14)	26 (19)	67 (18)		53 (19)	38 (90)
21	M	18	Right temporal lobectomy	Left homonymous upper quadrantic defect	58 (19)	95 (14)	74 (19)	83 (18)	67 (18)	67 (21)	72 (109)
22	M	30	Right temporal lobectomy	Partial left homonymous hemianopia	42 (19)	63 (15)	63 (19)	78 (18)	11 (18)	30 (21)	56 (108)

* Values in brackets refer to the number of " transformed " scores on which any index is based.

of confidence) also exclude the effect of the abnormal results at flicker fusion and local adaptation in cases with frontal pathology (see below).

The relative frequencies of the negative transformed scores relating to thresholds taken in the half-field of vision on the same and on the opposite side to a unilateral lesion were also compared in this group of cases. Performance on all the tests excepting only local adaptation was found to be very slightly more depressed in the half-field contralateral to the lesion than in the ipsilateral half-field. Statistical analysis, however, failed to demonstrate that this difference in performance between the two half-fields on all the tests is significant at the conventional 5% level of confidence.

The results in Group B are presented in Table IV. As expected, visual discrimination is more severely impaired in this group than in Group A, the mean overall efficiency index being only 54. On the other hand, the presence of perceptual disorder additional to field defects is not associated with a significant further loss of visual efficiency. Thus the mean overall efficiency index of the eight patients in Group C (Table V) is 51, only three points below

TABLE V

EFFICIENCY INDICES FOR INDIVIDUAL TESTS AND FOR ALL TESTS IN COMBINATION IN CASES WITH FIELD DEFECTS AND PERCEPTUAL LOSS (GROUP C)

Case	Sex	Age	Diagnosis	Field Defects	Perceptual Disorders	Efficiency Indices (normal = 100)						
						B.D.	F.F.	Ac.	L.A.	T.A.	A.M.	Overall
23	M	52	Bilateral occipital infarcts	Bilateral paracentral scotoma in upper quadrants; L. upper quadrantic defect	Prosopagnosia, achromatopsia, topographical loss	42 (19)*	38 (14)	26 (19)	94 (18)	22 (18)	41 (17)	36 (106)
24	M	63	Occlusion of basilar artery	R. homonymous hemianopia	Visual alexia	32 (19)	53 (15)	11 (18)	100 (18)	28 (18)	27 (15)	33 (103)
25	M	53	Cortical atrophy	L. lower quadrantic defect in L. eye	Simultanagnosia, visual constructive defects	37 (19)	67 (15)	100 (1)	89 (18)		87 (23)	74 (76)
26	M	49	Supratentorial meningioma	Concentric constriction more marked to L.	Visual constructive defect	37 (19)	33 (15)	26 (19)	11 (18)	11 (18)	50 (20)	32 (110)
27	M	49	R. parietal cystic glioma	L. homonymous attention hemianopia	Unilateral visual neglect, visual-spatial agnosia, topographical loss	74 (19)	89 (15)	32 (19)	100 (18)	22 (18)	75 (24)	65 (113)
28	M	61	R. parietal angioma	L. homonymous hemianopia	Unilateral visual neglect, visual-spatial agnosia	21 (19)	67 (15)	26 (19)	67 (18)	44 (18)	67 (21)	47 (110)
29	F	51	R. occipito-parietal glioma	Partial L. homonymous hemianopia	Visual-spatial agnosia, topographical loss	47 (19)	47 (15)	58 (19)	67 (18)	44 (18)	71 (21)	59 (110)
30	M	49	Cortical atrophy	R. homonymous hemianopia	Multiple defects of visual perception, dementia	11 (19)	77 (15)		83 (18)			61 (52)

* Values in brackets refer to the number of " transformed " scores on which any index is based.

the mean value for Group B. Individual results for patients in this group, and their significance in relation to the origins of agnosia, are discussed below.

The results given by all patients on all tests are analysed in order to determine the relative sensitivity of the different tests as indicators of visual loss. The mean efficiency indices of all patients and of Groups A, B, and C separately on each test are given in Table VI. It will be seen that tachistoscopic

TABLE VI

SENSITIVITY OF TESTS AS INDICATORS OF VISUAL DEFECT FOR ALL PATIENTS AND FOR GROUPS A, B, AND C SEPARATELY

	Mean Efficiency Indices (normal = 100)			
	All Cases	Group A	Group B	Group C
(1) Tachistoscopic acuity	46	72	32	29
(2) Flicker fusion	56	67	40	59
(3) Brightness discrimination	59	89	43	38
(4) Acuity for small objects	65	85	48	30
(5) Apparent movement perception	69	82	68	60
(6) Local adaptation	100	125	87	76

acuity appears the most, and local adaptation the least, sensitive indicator of defect in visual discrimination when all 30 patients are combined. In the cases of Group A, however, the lowest score is found on the test of flicker fusion. This alteration in the order of sensitivity of the tests is probably the result of a predominance of cases with frontal pathology in Group A (see below). The most striking finding in the cases of Group C is the depression of performance on three tests (T.A., Ac, and B.D.) in combination relative to the scores on the remaining three tests. Such a difference is not seen in either Group A or B, and it is most marked on the tests of acuity for small objects and brightness discrimination. For the scores on these two tests are relatively high in Groups A and B, whereas the mean efficiency index at tachistoscopic acuity is uniformly low for all 30 patients.

Differential analysis by site and laterality of lesion reveals only one significant difference of performance on the discrimination tests between appropriate sub-groupings of patients, when the presence of field defects is allowed for by taking a relative measure between the overall efficiency index and that relating to any specific test. Thus a significant increase in length of fading times on the local adaptation test is found in cases of exclusively frontal-lobe pathology. Nevertheless, prolongation of fading times is not entirely confined to frontal cases and may be demonstrated to be in excess of control results for all 30 patients in combination (χ^2 — 122, 1 d.f.). Patients with frontal lesions, moreover, tend towards low thresholds and small deviations of successive judgments on the flicker fusion test in comparison with the results given by patients with lesions elsewhere. This difference is, however, just below significance at the 5% level of confidence. The converse trend on the test of brightness discrimination, namely for frontal cases to score more highly than patients with temporal lobe lesions (but excluding cases with perimetric defects), also fails to prove statistically significant.

Discussion

We may now inquire what light our results throw upon the origin of agnosic disorders. As we have seen, some degree of sensory deficit has been established in 12 cases of cerebral lesion in the absence of visual field defects. Where field defects are present, moreover, an even greater sensory deficit, as established by our methods of examination, was ascertained in 10 cases. On the other hand, no significant increase in sensory deficit could be established in eight cases in which field defects were associated with higher perceptual disorders. It would therefore appear, on first inspection at least, that sensory deficits of the type adduced by Bay as responsible for visual agnosia do not play a significant role in the genesis of this disorder.

At the same time, it must be borne in mind that no true case of visual object agnosia in the classical sense of the term is included in our series. In the one case of " prosopagnosia " (Case 23), moreover, the overall efficiency index was undoubtedly low. This might be interpreted as evidence in support of Bay's view that defects in physiognomic recognition arise on a sensory basis. None the less, three patients in our series (Cases 19, 24, and 26) gave evidence of an even greater reduction in sensory efficiency without the least trace of prosopagnosia.* It is also noteworthy that one patient (Case 18) gave no evidence of visual agnosia at a time at which fluctuating alterations of sensory function were present over the entire visual field. Further, the combination of sensory defects and intellectual loss in certain of our patients (in particular Cases 19 and 20), was not found to give rise to agnosia in the manner suggested by Bay. It would therefore appear that impairment of visual discrimination, while present in many cases with disturbances in visual perception, is not in itself adequate to provoke the symptoms of agnosia.

The results in three cases presenting the syndrome of visual-spatial agnosia (as defined by McFie, Piercy, and Zangwill, 1950) do not suggest that sensory defects are of appreciable significance in its origin. The overall efficiency indices of three patients who presented this syndrome (Cases 27, 28, and 29) are respectively 65, 47, and 59. Although these values are low, they are certainly well above those given by several patients in Group B who had sustained field defects unaccompanied by spatial loss. Moreover, no consistent relationship between any one pattern of sensory deficit and visual-spatial agnosia can be detected. It would therefore appear that there is no direct association between reduction of visual efficiency and disorders of spatial judgment.

It might still be argued that the various disorders of visual perception are attributable to intellectual deficit of a global character. This claim cannot be fully discussed in the present context, but intellectual testing (fully reported elsewhere) revealed no greater intellectual impairment in cases comprising Group C than in either Group A or B. It is therefore unlikely that higher disorders of perception are the expression of global intellectual loss.

In connexion with Bay's reliance on the method of local adaptation, it should perhaps be pointed out that successive fading times determined at the same position in the visual field commonly vary considerably, even in healthy subjects. Thus variations of up to 31 sec. between successive fading times are normal at 2·5°, and of up to 10 sec. at the 15° positions. Moreover, this method has been shown to discriminate the least successfully of our tests between healthy and brain-damaged individuals. Its reliability, as indicated by test-retest correlation, is also lower than that of any other test excepting acuity for small objects. It may therefore be suggested that future studies of the significance of sensory defects in agnosia should not be limited to the use of this test alone.

The level of the neurophysiological changes in the visual system underlying the sensory deficits established in this study provides an important problem for future investigation. Whether, for example, local adaptation is peripheral or cerebral in origin is not at present known with certainty. The extent to which the defects described in this paper are specific to the visual modality has also to be ascertained. All that can be said with confidence is that defects in visual discrimination are commonly encountered in cases of cerebral lesion and may be elicited in perimetrically normal areas of the visual field. We are thus able to confirm Bay's finding that bilateral visual discrimination defects may follow unilateral cerebral lesions. We cannot, however, find confirmation of his view that such defects play an appreciable part in the genesis of the visual agnosias.

Summary

An investigation of visual sensory discrimination in 30 cases of brain lesion is reported. The object was first to determine the incidence and magnitude of sensory deficits in cases of cerebral lesion; and secondly to assess their significance in relation to the visual agnosias.

* It can of course be held that the precise distribution of sensory loss in the visual fields has greater significance for agnosia than overall reduction in visual efficiency. Thus in the case under discussion, it might be argued that the combination of paracentral scotomata with sensory deficit in perimetrically normal areas of the peripheral field is sufficient to constrain prosopagnosia. This interpretation is not, however, supported by Pallis (1955) in his discussion of this case.

The cases fall into three groups on the basis of the presence of field defects and/or higher perceptual disorders. All patients were tested on a variety of visual discrimination tasks at representative points in the visual fields. Their results were evaluated with reference to the thresholds given by a large control group.

The presence of visual sensory deficits in perimetrically normal areas of the visual field, both ipsilateral and contralateral to the side of a unilateral lesion, was ascertained. The results did not, however, support the view that agnosic conditions are secondary to deficits of visual sensory discrimination.

I wish to thank the physicians and surgeons of the National Hospital, Queen Square, for permission to study the cases under their care; likewise Dr. W. Ritchie Russell, of the Radcliffe Infirmary, Oxford, and Dr. C. A. Pallis, of the Royal Infirmary, Cardiff, who generously allowed me to investigate their patients at the National Hospital. I am also indebted to Dr. Eliot Slater for special facilities. My especial gratitude is due to Prof. O. L. Zangwill for his constant encouragement, help, and advice.

The late Dr. L. C. Thomson, of the Institute of Ophthalmology, kindly gave me help in designing the optical system and made available certain optical equipment on loan. I am also extremely grateful to Mr. H. B. Morton who helped with the design and construction of parts of the electrical equipment (by kind permission of Dr. W. A. Cobb); to Mr. J. W. Whitfield for his valuable advice on statistical problems; to Mrs. E. Warrington for assistance with the analysis of the data; and to Dr. A. Elithorn for his assistance in preparing this paper.

References

Bay, E. (1950). *Agnosie und Funktionswandel.* Springer, Berlin.
—— (1953). *Brain*, **76**, 515.
Critchley, M. (1953). *The Parietal Lobes.* Arnold, London.
Ettlinger, G. (1955). Ph.D. Thesis submitted to London University.
—— (1956). *Quart. J. exper. Psychol.* In the press.
Faust, C. (1951). *Nervenarzt*, **22**, 176.
—— (1955). *Die Zerebralen Herdstörungen bei Hinterhauptsverletzungen.* Georg Thieme, Stuttgart.
Jaffe, R. (1955). *A.M.A. Arch. Neurol. Psychiat.*, **73**, 57.
Jung, R. (1951). *Nervenarzt*, **22**, 192.
Leibowitz, H. (1954). *Amer. J. Psychol.*, **67**, 530.
McFie, J., Piercy, M. F., and Zangwill, O. L. (1950). *Brain*, **73**, 167.
Pallis, C. A. (1955). *Journal of Neurology, Neurosurgery and Psychiatry*, **18**, 218.
Russell, W. R. (1951). *Proc. roy. Soc. Med.*, **44**, 341.
Scheller, H. (1951). *Nervenarzt*, **22**, 187.

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 308

INAPPROPRIATE AFFECT

BY

ARTHUR HARRIS AND MARYSE METCALFE

From Bethlem Royal Hospital and the Maudsley Hospital and the Institute of Psychiatry, University of London

An inability to react emotionally and to " feel " in the highest sense of the word is a disturbance, the concept of which has evolved slowly in psychiatry and has come to assume ever-increasing importance. The grosser degrees of the condition have been known for a long time and recognized as a sign of unfavourable outcome. Thus over 100 years ago, in 1838, Esquirol wrote, " When the sensibility of lunatics is so weakened that they can look at the sun, that they have lost taste and smell, and that they remain unmoved by all discomforts, they will not get well ". From Kraepelin's classic account of dementia praecox which first appeared in the earlier edition of his textbook at the end of the nineteenth century, it is clear that he regarded this affective change as one of the cardinal features of this disease entity, for he described not only such signs as causeless, inappropriate laughter, but also subjective complaints of emotional emptiness and lack of feeling (Kraepelin, 1919). At the beginning of this century lack of affect began to attract serious detailed discussion. Stransky described a disturbance of coordination between the intellectual attributes of the whole psyche and the affective attributes, which he called intrapsychic ataxia (Stransky, 1909). Bleuler, in his famous monograph on dementia praecox first published in 1910, built up a vivid clinical picture with illustrative examples from patients he had seen (Bleuler, 1950). He regarded lack of affect as a bad prognostic sign and evidence of chronicity, remarking that " it has been known since the early years of modern psychiatry that an acute curable psychosis became chronic when the affects began to disappear ". For him it is one of the primary signs of schizophrenia and peculiarly typical of that ill-defined group. He recognized that it frequently appears in organic dementias, although it is then overshadowed by changes in the cognitive sphere. Bleuler was the first to observe that these patients have not in fact lost the capacity to react emotionally, but that they react in an unusual and frequently incomprehensible way. We can confirm this from our own experience, having a vivid recollection of several very chronic schizophrenic mental hospital inmates whose affect appeared to have been lost, but who showed all the signs of fear in an exaggerated form when confronted with a Benedict-Roth basal metabolism apparatus (Harris, 1938). This observation has been further borne out by recent experimental work (Malmo, Shagass, and Smith, 1951). The most accurate term for the affect in these patients is " inappropriate ", but we prefer to use as a rule the more convenient word " flat ".

Affective flattening has also been described as a reversible phenomenon produced by oxygen lack (McFarland, 1932; Hoskins, 1937), and by von Economo in encephalitis lethargica (von Economo, 1931). Some attempts have been made to explain it. Thus Kant (1942) regarded it as a reaction of frustration to mental disintegration and loss of capacity for normal responses. Abély and Abély (1932), after trying to distinguish disturbances in the separate spheres of mood, emotion, and feelings, decide that the phenomena are all explicable on the basis of a failure of association in the Wundtian sense as postulated by Bleuler in the case of schizophrenic thought disorder. The orthodox Freudian view seems to be that it is a symptom of libidinal regression to the ego and of the consequent narcissism (Fenichel, 1934; Symons, 1941).

Bleuler's demonstration that the course of schizophrenic illnesses was variable and the outlook not uniformly bad led to various prognostic enquiries. In these the uniformity with which many different workers found affective flattening to be an adverse factor was striking (Strecker and Willey, 1924; Stalker, 1939; Malamud and Render, 1939; Gildea and Man, 1943). However, papers also appeared describing patients with affective flattening who did get well (Strecker and Willey, 1927; Rennie, 1941). A follow-up study, covering the whole group of the functional psychoses, found it to be the one clinical sign of definitely grave prognostic significance, although in 11% of the patients who showed it the disease ran a favourable course (Harris and Norris, 1954). Many of these authors made it clear that it is not a feature of many illnesses diagnosable as

schizophrenia by the criteria usually employed but textbooks continue to describe it as an essential ingredient of that condition. Collins therefore found it necessary to publish descriptions of patients whom most psychiatrists would regard as schizophrenic, but who retained warm affective responses and good emotional contact with the examiner (Collins, 1943).

There is a risk of ambiguity in the discussion of impaired capacity for emotional responses, as various distinct clinical entities can be regarded as occurring in this way. There is the type of character disturbance which manifests itself as a lack of sustained and consistent emotional attitudes in personal relationships, in occupations, and in aims which should influence conduct over long periods. This is seen in many persons classified as psychopaths or hysterics, and is usually recognizable from the patient's own history, although hints of it may emerge in the course of the first interview. In the classical hysterical *belle indifference* the emotional lack is more apparent than real, and the patient's state becomes comprehensible and appropriate when the role played by his symptoms and the purpose of his illness are understood. The subjective sensation of loss of feeling and inability to react emotionally is frequently spoken of by patients, who are more likely in that case to be suffering from some variety of neurotic or milder depressive condition than frank psychosis, although occasionally schizophrenics and other psychotics will make this complaint. It is a particular feature of syndromes of depersonalization (Schilder, 1928; Ackner, 1954).

The condition that we are concerned with here is a matter of clinical observation and depends on the interpretation of the patients' facial expression, their tone of voice, and the content of their talk. One would think at first sight that these signs are extremely susceptible to differences of opinion. Indeed, Muncie describes at some length the difficulties encountered in the normal recognition of emotions (Muncie, 1948), but Hebb, on the other hand, has strongly defended the use of this recognition in scientific work (Hebb, 1946). Strecker and Willey (1927) describe a spurious affective flattening due to lifelong habits of evasiveness, a personality steeled against any display of feeling and the like, which can be misleading if care is not taken. In practice, however, a surprisingly high measure of agreement is obtainable. Miller, Clancy, and Cumming (1953), in their efforts to assess the mental state of patients by correlating reports from large numbers of different observers, found that the mood of the patient was the item on which there was the nearest approach to unanimity of opinion. There was far more disagreement in their series over such an apparently straightforward matter as the tidiness or untidiness of the patient's dress.

Assessment by Clinical Observation

A crucial test for the reality of this phenomenon of affective flattening seems to be the presence or otherwise of agreement among independent observers as to its existence in a given patient. We rated 20 schizophrenic patients independently on the scale—no affective flattening, moderate affective flattening, gross affective flattening or incongruity—and found that we agreed in 19.

Then we availed ourselves of the opportunity afforded by an investigation into therapeutic results which involved the assessment of schizophrenic patients each by three separate psychiatrists to ascertain the extent of agreement among these three pscyhiatrists concerning the patient's affective state. The psychiatrists sat together and interviewed the patients one at a time. After the interview each psychiatrist was given a form with spaces for the date, the patient's name and the doctor's name, and the following words:

Affective state (circle appropriate term).....
.....Elated
.....Depressed
.....Normal
.....Moderately flat
.....Grossly flat or incongruous

Each completed this form without discussing it with the others.

For the sake of simplicity and clarity and because it is adequate for our purpose, we may take the results on a three-point scale: (1) Grossly flat; (2) moderately flat affect; (3) absence of flattening of affect, including in this group those patients with normal affect and those showing elation or depression. It will be remembered that in the previously mentioned follow-up enquiry neither elation nor depression had an adverse effect in regard to the outcome of the illness (Harris and Norris, 1954).

Out of 23 patients, there was complete agreement between the three assessors in 17, four being rated as grossly flat, seven as moderately flat, and six as showing no affective flattening. In each of the remaining six, two assessors had agreed that the patient's affect was in the moderately flat category, although in four a third assessor had made a rating of absence of affective flattening and in two of grossly flat affect. It is only in the middle ranges, therefore, that there are discrepancies. It seems probable that we are dealing with a continuous scale from absence of affective flattening to the grosser degrees of the disorder, with areas of transition between our inevitably rather artificial three points in which there is scope for disagreement.

There is some evidence that intensity of affect, without regard to the special abnormal quality with which we are dealing in this paper, is of prognostic importance, so that patients who are depressed or agitated or elated have a better chance of recovery (Bayard and Pascal, 1954; Schofield, Hathaway, Hastings, and Bell, 1954); indeed, Harris and Norris's figures could be interpreted in this

way. It is of interest, therefore, to examine the problems of assessment which an investigation into this point would raise and the extent of agreement achieved by our three psychiatrists in this respect. No patients were thought to be elated, there was complete agreement that three patients were depressed, and that one had normal affect, and in the remaining two patients without affective flattening, two of the assessors rated their affect as normal and one as depressed. In the two last patients, the same assessor rated both as depressed and he had also rated one of the patients, whom the other two had regarded as moderately flat, as depressed, so that he appeared to have a bias in favour of depression. There is scope for disagreement in the interpretation of the signs of depression, which one observer might regard as indicative of a persistent, pathological affect, and another as a natural reaction to the discussion of the patient's unenviable plight during the interview. It is clear that the estimation of intensity, or more precisely whether that intensity has passed the bounds of the normal, is more difficult than that of the peculiar change with which we are concerned at present. This estimation only becomes important if one is regarding the intensity of affect without regard to its appropriateness as the thing to be determined as some workers have done (Bayard and Pascal, 1954; Schofield *et al.*, 1954).

The three psychiatrists were all products of the same training school, although they had received their training at different times. The experiment was repeated with three house physicians, who were in their first six months of psychiatric training, and nine schizophrenic patients. The house physicians were only in agreement on three patients, and in the remaining six, no less than four were regarded as having grossly flat affect by one observer, and no affective flattening by another. It is clear, therefore, that training and experience are necessary before a reliable evaluation can be given. The ratings must be made at the same time as, especially in acute psychoses, changes may be rapid.

Characteristics of Patients Showing Affective Flattening Compared with Other Schizophrenic Patients

It is of interest to see how a large group of patients showing affective flattening differ from a group of other schizophrenic patients. For every in-patient in the Bethlem Royal and Maudsley Hospitals a document called an item sheet is filled up. On this is recorded a mass of clinical information regarding the history, state on examination, investigations performed, and outcome. The sheets are completed by the house physicians and registrars, *i.e.*, junior doctors undergoing psychiatric training, and checked by the physicians on the senior staff. One of the items recorded is the presence of affective flattening or incongruity. We examined the item sheets of all the patients who had been diagnosed as schizophrenic, admitted to the wards over a period, divided them into two groups on the basis of whether they had or had not shown affective flattening or incongruity, and sought for significant differences between the two groups. Age on admission, sex, psychiatric family history, early life and childhood development, medical history, clinical signs, treatment given, and outcome, were considered. The only significant differences were found in the fields of age, clinical signs, and outcome.

TABLE I

DIFFERENCES BETWEEN PATIENTS WITH AFFECTIVE FLATTENING AND OTHER SCHIZOPHRENICS

	Not Affectively Flat	Affectively Flat	*Value for P
Total number	235	178	—
Age group 10-19	15	29	0·01
Overactive	29	38	0·02
Impulsive or unpredictable	45	77	0·001
Posturing, grimacing mannerisms, stereotype	48	87	0·001
Schizophrenic type of thought disorder	99	129	0·001
Delusions of influence or passivity	64	79	0·001
Visual hallucinations	17	38	0·001
Auditory hallucinations	83	94	0·001
Outcome:			
Recovered or much improved	113	60	0·01
Slightly improved or no change	116	104	—
Worse	4	13	0·01

*Calculated by employing χ^2.

It will be seen that the affectively flat group suffered more from certain other severe psychotic symptoms, had a less favourable outcome, and had a higher proportion of teenagers.

Test Performance of Schizophrenics Showing Affective Flattening Compared with Other Schizophrenics

Possible views as to the nature of affective flattening are (1) that it is a highly specific disturbance not necessarily accompanied by other defects in mental functioning, or (2) that it is part and to some extent a measure of a general mental impairment. In the latter case, which seems to us the more probable, those patients who show affective flattening could be expected to give more evidence of deficit in other fields than those who do not.

For this part of the investigation our subjects were 40 patients, 22 women and 18 men, who all displayed gross psychotic symptoms of a classically schizophrenic kind, for example, bizarre delusions, hallucinations with a persecutory or fantastic content, passivity feelings, thought disorder, or fatuous, senseless behaviour in various combinations. They were purposely taken at random from patients under treatment at Bethlem Royal and the Maudsley Hospitals and included both in- and out-patients. It was considered undesirable to exercise any selection at this stage on such grounds as age or length of illness, as this selection might have obscured the natural incidence of these variables in groups differing with regard to flatness of affect, but patients with markedly dull intelligence were excluded.

Test Battery.—A series of psychological tests was given to each patient and within three days, either before or after being tested, each patient was interviewed by the psychiatrist who rated him or her according to the three categories of affect.

Wechsler-Bellevue Test.—A shortened version of the

Wechsler-Bellevue test, *i.e.*, vocabulary, similarities, and block design subtests, was included because of its satisfactory correlation with the complete test (Hilden, Taylor, and Dubois, 1952).

The Rampton Hospital Sorting Test.—This is the latest version of a series designed to bring out deficiencies in capacity for abstraction (Hall, 1951; Tong, 1955). Cardboard pieces, which show similarities in colour, shape, or decoration, are given to the subject, who has to sort them in five different ways, the scores being inversely related to the number of clues needed to perform each task successfully.

The Nufferno Speed Test.—This in stressed and unstressed versions (Institute of Psychiatry, University of London, 1953) is one with which definite findings in the field of the functional psychoses have recently been achieved (Furneaux, 1953; Shapiro and Nelson, 1955).

The Recognition of Absurdities Test (Hunt, 1935).—This test consists of a text containing a certain number of absurdities which the subject is given to read. First he is asked what he thinks of the story. If he does not point out the absurdities he is asked to retell the story in his own words. The third step is to ask him if there is any way in which he could improve on it. The fourth step is to ask him outright whether he can find anything contradictory or absurd. Hunt compared a group of schizophrenics, a group of paretics, and a group of normals. The schizophrenics either never found the absurdities at all or only found them in the last two steps, in contrast to the group of paretics who found them much sooner, and the group of normals who found them all in the first reading.

Wegrocki's Tests.—The battery was completed by a series of tests used by Wegrocki and considered by him to be a measure of generalizing ability (Wegrocki, 1940). There were (*a*) a set of proverbs which have to be correctly matched with another set of equivalent proverbs and then with a corresponding set of explanations; (*b*) a list of analogies, the final word of which had been left out and had to be inserted by the subject, for example, "eat is to food as wear is to ....."; and (*c*) a list of essential differences where the subject has to underline the word which does not fit the others in a series of four, for example, camera, violin, piano, flute. Wegrocki had found that his schizophrenic patients tended, especially on the proverbs test, to fall into two groups, one which did almost as well as normals and one which did very much worse, paranoids gravitating to the former group and hebephrenics to the latter. This was promising from our point of view since it seemed likely that the hebephrenics would show a higher proportion of flat affects than the paranoids.

The whole battery took about four hours to administer and was given individually to each patient in two sessions of about two hours each. Cooperativeness was estimated on Shakow's scale (Shakow, 1946) and all our patients fell into the three highest grades, most of them being in the two highest grades. In fact, lack of cooperativeness did not seem to influence the results, although some patients were a little lethargic or apt to lose interest.

TABLE II

RESULTS OF BATTERY OF TESTS USED

Test	Means of Test Results			Level of Significance*	
	Grossly Flat Group	Moderately Flat Group	No Flatness Group	Between Three Groups	Between First and Third Groups
Wechsler-Bellevue (I.Q. score)	103	115	117	At 2%	At 2%
Proverbs (error score)	5·75	3·75	3·46	—	—
Essential differences (error score)	7·50	4·75	6·37	—	—
Analogies (error score)	10·16	8·33	7·37	—	—
Sorting	17·33	20·33	21·56	At 7%	—
Absurdities (mean no. of absurdities)	4·1	4·5	6·1	—	—
Nufferno speed (unstressed) (time for solution)	1·235	1·116	1·083	Almost at 5%	At 5%
Nufferno speed (stressed) (time for solution)	1·156	0·920	0·994	Almost at 5%	At 5%
Wechsler-Bellevue subtests:					
Vocabulary (weighted score)	11	11·5	11·8	—	—
Similarities (weighted score)	9·8	11·4	10·6	—	—
Block design (weighted score)	8·3	11·5	12·3	Beyond 1%	Beyond 1%
Block design (right solutions)	17·7	20·2	18·5	—	—
Block design (speed credits)	−0·9	+5·5	+6·9	Beyond 1%	Beyond 1%

*For test of significance employed see A. R. Jonckheere (1954).

Results

The results (Table II) are in the expected direction inasmuch as on all tests the mean scores of the grossly flat affect group are inferior to those of the normal group and on all tests but two the grossly flat affect group are inferior to the moderately flat, which in turn are inferior to the normal affect group. The significance of these differences is calculated by a method suitable for studying trends in small groups where the scores do not assume a normal distribution (Jonckheere, 1954). The Wechsler-Bellevue and the Nufferno speed tests differentiate most significantly between the groups. Further analysis of the Wechsler-Bellevue test shows that the difference is due mainly to a poor performance on the block design subtest. This difference alone is significant far beyond the 1% level when the three groups are compared. On the vocabulary and similarities subtests there is scarcely any difference at all between our groups. In the block design subtest the scores were separated into those obtained for correct solutions and those obtained for speed. The results show that it is not the accuracy of the performance but only its speed which is very much lessened in the flat affect group.

Data exist on the Nufferno speed tests for normal

subjects and for psychotic patients. Our groups with no affective flattening and moderate affective flattening score at the same level as the 50th percentile of these normal subjects, whereas our grossly flat affect group scores just below the 30th percentile of the normals. Our grossly flat affect group performs approximately at the same level as the average for the previously tested psychotics, whereas both the groups without flat affect and with moderately flat affect perform better than these psychotics (Furneaux, 1953).

It is clear, then, that the patients with flat affect show a deterioration in mental speed and this is the most striking finding of this part of the enquiry. The different measures for speed are obviously intercorrelated and the levels of significance obtained between the groups for each of these measures should not be considered as independent from each other.

The Rampton Hospital sorting test differentiates between our groups at a level approaching satisfactory significance. This test is distinguished from the others by demanding a certain degree of inventiveness and by leaving the method of solution to the patient.

Neither Hunt's absurdities test nor Wegrocki's tests differentiate significantly between our groups. Our patients found more absurdities than Hunt's schizophrenics, averaging five as compared with his three. Even more striking is the finding that our patients discovered 28 absurdities, or 37% of the total, in the first step whereas his group found only one. Similarly with Wegrocki's tests our patients performed better than his schizophrenics, none of our patients falling into his high error category, although they did less well than his normal adult controls and showed a greater range of error scores. Wegrocki's description of the test behaviour of some of his patients and their lower I.Q. range and mean (90 as compared with our patients' 111) suggests that they included a higher proportion of very sick ones who before they fell ill had lower intellectual endowments than ours.

The possibility that factors other than flatness of affect had produced the differences between our groups in respect of speed must be considered. The groups show little appreciable difference regarding the age distribution although there are fewer very young patients in the " grossly flat " group. But they do differ in length of illness and the presence or absence of physical treatment. (Physical treatment consisted of insulin coma in all except one patient who had E.C.T. and one patient who in addition to insulin coma had a leucotomy.) The proportion of patients who had received physical treatment is higher in the " grossly flat " group than in the " moderately flat " group. The highest proportion of patients (62%) who had no physical treatment at all were in the " no flatness " group. In terms of length of illness the patients were divided into those of recent onset (less than one year), those who had been ill between one and two years, and those who had been ill for more than two years. The distribution of patients is the same in the first and second groups but in the third group (no flatness) there was a higher proportion of patients with illness of recent onset.

The subjects are too few for an analysis of variance, so an examination of the influence of these factors on one score only, the speed score of the block design test, was undertaken with the result that physical treatment and length of illness appeared to have no adverse effect on this score (Table III). Nevertheless, considering the smallness of the groups, the possibility that some of the variables which we purposely did not control may have affected the result must be kept in mind.

Discussion

The findings that groups of schizophrenic patients with flat affect when compared with groups of schizophrenic patients without flat affect show a higher incidence of other serious symptoms, a poorer performance on psychological tests involving intellectual processes, and a less satisfactory outcome

TABLE III

COMPARISON OF BLOCK DESIGN SPEED CREDIT SCORES FOR GROUPS WITH VARIED INCIDENCE OF PHYSICAL TREATMENT AND VARYING LENGTHS OF ILLNESS*

	Grossly Flat Group		Moderately Flat Group		No Flatness Group		Total No. of Subjects	Average Score
	No. of Subjects	Average Score	No. of Subjects	Average Score	No. of Subjects	Average Score		
Physical treatment within past 6 months	3	−0·7	4	7	4	10·2	11	6
Physical treatment but not within past 6 months	6	0	4	5·8	2	9·5	12	3·4
No physical treatment	3	−5·7	4	3·7	10	5·1	17	2·8
Illness less than 1 year	3	−4	3	3·7	7	7·2	13	3·8
Illness between 1 and 2 years	2	−3	2	7	4	7·2	8	4·6
Illness longer than 2 years	7	0·4	7	5·8	5	6·2	19	3·9

*Physical treatment and length of illness as such have no adverse influence on block design speed credit scores.

to their illness are consistent with the view that affective flattening is indicative of a severer degree of illness and a greater impairment of mental functioning. The fact that deficit is most clearly demonstrable in the field of speed agrees well with the results of other investigations which show that slowing is the abnormality most easily brought out by present test methods in patients suffering from functional psychoses (Shapiro and Nelson, 1955). Babcock suggested 20 years ago that the apparent lack of emotion in schizophrenia may be due to slowness of response (Babcock, 1933). It is not impossible that speed alone is the responsible factor. The phenomenon of flattening of affect is due to an observer/subject interaction and it may arise from the subject being slower than the observer. This poses the further question as to what produces the slowness. A man may walk slowly because of muscular weakness, cerebellar ataxia, sensory loss, grief, or mental preoccupation. Further work must be directed towards the precise identification of the mental function concerned.

Summary

The phenomenon of inappropriateness of affect in schizophrenic subjects has been investigated. Trained observers show a high degree of agreement in rating individual patients for its presence or absence. Groups of schizophrenics who exhibit inappropriate affect, when compared with groups of schizophrenics who do not, have a higher incidence of other serious symptoms, a poorer performance in psychological tests, and a less satisfactory outcome to their illness. The deficit in the tests is mainly in the speed at which they solve problems.

We are indebted to Drs. Ackner and Oldham for help in the investigation of the reliability of psychiatrists' ratings and to the Board of Governors of Bethlem Royal Hospital and the Maudsley Hospital who have financed this investigation from their research fund.

References

Abély, X., and Abély, P. (1932). *Ann. méd.-psychol.*, **90** (1), 511.
Ackner, B. (1954). *J. ment. Sci.*, **100**, 838.
Babcock, H. (1933). *Dementia Praecox : A Psychological Study.* Science Press, Lancaster, Pa.
Bayard, J., and Pascal, G. R. (1954). *J. consult. Psychol.*, **18**, 122.
Bleuler, E. (1950). *Dementia Praecox*, trans. by Zinkin, J. International Universities Press, New York.
Collins, R. T. (1943). *J. ment. Sci.*, **89**, 27.
Economo, C. von (1931). *Encephalitis Lethargica : Its Sequelae and Treatment.* Oxford University Press, London.
Esquirol, E. (1838). *Des maladies mentales.* Baillière, Paris.
Fenichel, O. (1934). *Outline of Clinical Psychoanalysis.* New York.
Furneaux, W. D. (1953). Nuffield Research Unit Internal Report F.1, Part 2.
Gildea, E. F., and Man, E. B. (1943). *Amer. J. Psychiat.*, **99**, 496.
Hall, K. R. L. (1951). *Brit. J. med. Psychol.*, **24**, 118.
Harris, A. (1938). *J. ment. Sci.*, **84**, 735.
——, and Norris, V. (1954). *Ibid.*, **100**, 727.
Hebb, D. O. (1946). *Psychol. Rev.*, **53**, 88.
Hilden, A. H., Taylor, J. W., and Dubois, P. H. (1952). *J. clin. Psychol.*, **8**, 321.
Hoskins, R. G. (1937). *Arch. Neurol. Psychiat. (Chicago)*, **38**, 1261.
Hunt, J. McV. (1935). *Amer. J. Psychol.*, **47**, 458.
Jonckheere, A. R. (1954). *Brit. J. statist. Psychol.*, **7**, 93.
Kant, O. (1942). *J. abnorm. soc. Psychol.*, **37**, 398.
Kraepelin, E. (1919). *Dementia Praecox and Paraphrenia.* Livingstone, Edinburgh.
McFarland, R. A. (1932). "The Psychological Effects of Oxygen Deprivation (Anoxemia) on Human Behaviour." *Arch. Psychol. (N.Y.)*, No. 145.
Malamud, W., and Render, N. (1939). *Amer. J. Psychiat.*, **95**, 1039.
Malmo, R. B., Shagass, C., and Smith, A. A. (1951). *J. Personality*, **19**, 359.
Miller, D. H., Clancy, J., and Cumming, E. (1953). *Psychiat. Quart.*, **27**, 439.
Muncie, W. (1948). *Psychobiology and Psychiatry*, 2nd ed. Mosby, St. Louis.
Rennie, T. A. C. (1941). *Arch. Neurol. Psychiat. (Chicago)*, **46**, 197.
Schilder, P. (1928). "Introduction to a Psychoanalytic Psychiatry." *Nerv. ment. Dis. Monograph Series*, No. 50. Nervous and Mental Disease Publishing Co., New York.
Schofield, W., Hathaway, S. R., Hastings, D. W., and Bell, D. M. (1954). *J. consult. Psychol.*, **18**, 155.
Shakow, D. (1946). *The Nature of Deterioration in Schizophrenic Conditions.* Coolidge Foundation, New York.
Shapiro, M. B., and Nelson, E. H. (1955). *Brit. J. med. Psychol.*, **28**, 239.
Stalker, H. (1939). *J. ment. Sci.*, **85**, 1224.
Stransky, E. (1909). *Über die Dementia Praecox.* Bergmann, Wiesbaden.
Strecker, E. A., and Willey, G. F. (1924). *Amer. J. Psychiat.*, **80**, 592.
——, —— (1927). *J. ment. Sci.*, **73**, 9.
Symons, N. J. (1941). *Brit. J. med. Psychol.*, **18**, 344.
Tong, J. E. (1955). *Brit. J. med. Psychol.*, **28**, 19.
Wegrocki, H. J. (1940). "Generalizing Ability in Schizophrenia." *Arch. Psychol. (N.Y.)*, No. 254.

BOOK REVIEWS

The Spino-cerebellar Degenerations. By J. G. Greenfield. (Pp. xi + 112. 17*s.* 6*d.*) Oxford: Blackwell Scientific Publications. 1954.

The spino-cerebellar degenerations are amongst the most puzzling of all diseases of the nervous system, and in giving us a full review of the literature Dr. Greenfield has done neurologists a considerable service. The histological aspect is covered very fully, and many interesting clinical features of these conditions are described and discussed. The one feature in the book which is slightly disappointing is the fact that the pathological aspects are treated very briefly, when one had hoped that Dr. Greenfield's great knowledge would have given the pathological side of the problem a unique and invaluable position.

However, the book will be of permanent value and should be on the shelves of all who are interested in disorders of the cerebellum.

Das Schädelhirntrauma. By Erich Katzenstein. (Pp. 992; 592 figures. Sw. Fr. 68.-.) Basel: Benno Schwabe. 1955.

This formidable study is based on clinical and pathological material from cases of head injury collected during the past 20 or 30 years in the Monakov Institute of Brain Anatomy, Zurich.

There are detailed pathological studies of 81 fatal cases, including cases of birth trauma, which occupy 600 pages of the book. It is perhaps surprising that so much should be expected of visible lesions when the modern emphasis is more on what Jefferson called " invisible contusion " of the nervous elements. It is not surprising to find, therefore, that though the historical introduction, and the case records are very complete, the discussion is in many respects disappointing.

The absence of an index greatly reduces the value of the book.

Das Hirntrauma. Edited by E. Rehwald. (Pp. xii+528; 106 figures. DM. 44.-.) Stuttgart: Georg Thieme Verlag. 1956.

This publication reports the proceedings of a recent conference on brain injuries at which over 50 papers were given. The result is disappointing, for many important aspects of brain wound are not considered at all, and few of the papers add much to existing knowledge.

Handbuch der speziellen pathologischen Anatomie und Histologie. Edited by O. Lubarsch, F. Henke, and R. Rössle. Part IV: **Erkrankungen des zentralen Nervensystems,** edited by W. Scholz. (Pp. 947; 451 figures, 5 tables. DM. 294.-.) Berlin, Gottingen, Heidelberg: Springer Verlag. 1956.

The high standard of the critical reviews contained in this volume maintain those expected of this well-known *Handbuch*. There are valuable chapters on the pathological findings in mental disease such as dementia praecox and manic-depressive psychosis, also in mental deficiency, mongolism, and epilepsy. The section on birth injuries is impressive, but the article on congenital malformations is not so clear, and some of the descriptions (*e.g.*, of the Arnold-Chiari malformation) are inaccurate. This section contains a useful list of references to published accounts of human embryos with abnormalities of the nervous system.

The chapter on hydrocephalus includes an account of internal herniations due to tumours, and also of disease of the dura mater and of the choroid plexus.

Tumores Intracraneales. Monografia del Instituto Nacional de Oncologia, edited by S. Obrador Alcalde and J. Sanz Ibanez. (Pp. 464; 222 figures.) Madrid. 1955.

In the summer of 1955 the National Institute of Oncology held a summer course at Santander which was in substance a symposium on intracranial tumours. The majority of the contributors were Spanish but there were a number of distinguished foreigners, such as Lima speaking on arteriography, Zulch on neuropathology, and Selverstone on the use of isotopes in diagnosis.

The present monograph is a record of the proceedings edited by S. Obrador Alcalde and J. Sanz Ibanez. It covers most aspects of the subject—pathology, special diagnostic methods, clinical features, and treatment. With the traditional excellence of the Spanish school in neuropathology, it is natural that this section is outstanding. The clinical sections are valuable as records of the individual contributors' own experience rather than mere textbook compilations, and they indicate a high standard of surgical practice in the Peninsula.

For those neurosurgeons who read Spanish this is an interesting and useful book of reference.

Hypothalamus und Thalamus. By W. R. Hess. (Pp. x + 70; 246 figures. DM. 36.-.) Stuttgart: Georg Thieme Verlag. 1956.

This book represents Part III of Professor Hess's " Studies on the Physiology of the Brain Stem ". This volume, which incorporates an English translation,

consists of illustrative photographs of cat brains with sites of stimulation indicated and a pictorial and verbal description of the response obtained. All the work has been with cats and is derived from the elegant technique that Professor Hess has elaborated for inserting indwelling electrodes in the living animal which can be stimulated at will during its normal life's activities. A variety of autonomic responses, simple and complex, and at times the complicated sequence of motor behaviour that accompanies them, can be elicited by appropriate stimulation of the thalamic and hypothalamic regions.

Regeneration in the Central Nervous System. Edited by William F. Windle. (Pp. vi + 311; 68 figures. 69*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1955.

This book is the result of a conference on the subject of its title sponsored by the American National Advisory Neurological Disease and Blindness Council. There are 25 chapters, each by different authors. The problem is reviewed throughout the animal kingdom, and in its biochemical and physiological aspects. Four chapters are devoted primarily to regeneration in man. It will be of interest to clinicians, for there is still a tendency in clinical teaching to state dogmatically that regeneration never occurs in the central nervous system. However, to the clinician the important point is whether any regeneration that occurs is likely to give worthwhile functional recovery, and whether any procedures can increase the range of such recovery. These points are also briefly considered.

Cardiovascular Innervation. By G. A. G. Mitchell; Foreword by Sir Geoffrey Jefferson. (Pp. xii + 356; 217 figures. 55*s*.) Edinburgh and London: E. & S. Livingstone. 1956.

The author of this important monograph is well known as an authority on the so-called autonomic nervous system. Although this work is primarily anatomical, other aspects including those of physiological and clinical interest are freely referred to. Finally there is a carefully prepared list of about 8,000 references which will be of great value to many research workers.

The Organization of the Cerebral Cortex. By D. A. Sholl. (Pp. xvi + 125; 12 plates, 12 diagrams. 18*s*.) London: Methuen; New York: John Wiley. 1956.

The rapidly increasing knowledge of the anatomy and physiology of nerve-cell arrangements must lead to revised conceptions of how the brain works. This present book comes from an expert on histological structure and contains some beautiful illustrations. The sections concerned with the physiological and clinical aspects are not so impressive, but the last chapter on theories of cortical organization contains some stimulating discussion with emphasis on the mathematics of the problem.

Masked Epilepsy. By Hugh R. E. Wallis. (Pp. x+51. 7*s*.) Edinburgh and London: E. & S. Livingstone. 1956.

This book sets out to prove that cyclical vomiting and what has been called the "periodic syndrome" in children, together with certain cases of episodic headaches, pyrexia, sleepwalking, nightmares, and night and day terrors are all forms of masked epilepsy. The evidence consists of a review of 20 cases (with mention of a further nine) of these conditions, in which there was either a family or personal history of epilepsy, or an abnormal electro-encephalogram (E.E.G.), together with clinical improvement on phenobarbitone medication in 18 cases and on primidone in two.

The canons of evidence accepted by the author are worth illustrating. In two cases cited (Nos. 15 and 16) recurrent abdominal pain occurred in one, and periodic fever with anorexia and irritability in the other. There was no family history or E.E.G. evidence of epilepsy, but in both symptoms improved with phenobarbitone. The author comments "the response to anticonvulsant treatment proves" that epilepsy was present. Such standards of evidence are unlikely to recommend this work widely. Nevertheless, the author considers that his evidence permits him to claim discovery "of the cause of a malady that has baffled the medical profession for three-quarters of a century".

Poliomyelitis. By W. Ritchie Russell, 2nd ed. (Pp. xi + 147; 40 figures. 16*s*.) London: Edward Arnold. 1956.

The first edition of this book, published in 1952, was the most useful account of anterior poliomyelitis from the neurological and therapeutic aspects which had appeared in recent years. This second edition is well up to the high standard of the earlier edition but is considerably longer. Most of the additional pages are devoted to an admirably clear account of the types of respiratory involvement which may occur in the disease and to the methods of managing them which the author has found most useful in his unit at Oxford, and more attention has also been given to the methods of treating weak and paralysed muscles after the acute phase of the illness. This book is eminently practical in its outlook and will continue to be of real value to anyone who is likely to treat patients suffering from poliomyelitis. There is a curiously ambiguous sentence about the use of gamma globulin on page 14; possibly the ambiguity is due to the unintentional omission of the vital word "not".

Correlative Neurosurgery. By Edgar A. Kahn, Robert C. Bassett, Richard C. Schneider, and Elizabeth C. Crosby. (Pp. xv + 413; 235 figures. 140*s*.) Springfield, Illinois; Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1955.

This book is prepared from discussions in the wards of the highly practical Neurosurgical Clinic of the University of Michigan Medical School. Thus it contains little of interest to the research worker, but, as Dr. Kenneth McKenzie says in the foreword, the young neurosurgeon will find in it a number of surgical tips which may help to keep the beginner out of trouble.

Clinical Studies in Neurology. By Harry L. Parker. (Pp. xiii + 364. 47*s.* 6*d.*) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1956.

This is an excellent record of a series of clinical demonstrations, each of which is presented as a human story which bears the hallmark of " good doctoring ". The racy account of the clinical problem is a pleasure to read and should prove to be both acceptable and stimulating to the student of neurology.

Practical Neurology. By L. M. Davidoff and E. H. Feiring. (Pp. xvii + 442. 52*s.* 6*d.*) London: McGraw-Hill; New York: Landsberger Medical Books. 1955.

This book is written by surgeons for the physician engaged in general practice. It gives a superficial account of various gross neurological syndromes, but many common conditions receive inadequate consideration, especially as regards differential diagnosis and treatment.

Neurological Nursing. By John Marshall. (Pp. ix + 166; 83 figures. 18*s.* 6*d.*) Oxford: Blackwell Scientific Publications. 1956.

This book fills a gap in neurological literature, for nowhere else can the nurse—or the doctor—obtain such clear advice on the nursing of neurological patients. The sub-heading of the book is " A Practical Guide ", but sufficient of the anatomical, physiological, and pathological background of neurological disease is described to indicate the rationale of the appropriate nursing care. There are many line drawings and photographs to illustrate both the correct procedures and the commoner mistakes. Of special significance are the chapters on the nursing of the unconscious patient and the management of respiratory difficulties, conditions in which incorrect care can so rapidly lead to disaster.

Progress in Clinical Psychology, Vol. II. Edited by Daniel Brower and Lawrence E. Abt. (Pp. viii + 364. $7.75.) New York: Grune & Stratton. 1956.

This is the second volume in a series designed to review and summarize recent work in clinical psychology. It must be said that this subject is conceived very much more broadly in the United States than in Britain and has come to comprise a wide variety of para-medical trades (less or more reputable) open to those with academic qualifications in psychology. Among them are psychometric and projective testing, counselling and psychotherapy, remedial teaching and rehabilitation of the disabled. Although not all these activities on the part of personnel untrained in medicine would be countenanced in this country, British psychologists working in the clinical field may well find some useful material in this volume. To the neurologist, however, there is little of value apart from Dr. Battersby's able review of higher visual defects.

It is instructive to learn that one of the editors of this volume has devised a procedure known as bibliotherapy. This apparently consists in the reading of psychological texts. Fortunately, perhaps, no data as to its efficacy are presented.

A Primer of Freudian Psychology. By Calvin S. Hall. (Pp. xii + 137. 13*s.* 6*d.*) London: George Allen & Unwin. 1956.

This book summarizes Freud's conception of normal as opposed to abnormal psychology. The author's aim is " to rescue Freud from the domain of mental disorders and to restore him to his legitimate place within the province of normal psychology".

Introduction to Psychopathology. By L. I. O'Kelly and F. A. Muckler. (Pp. xii + 704. 50*s.*) London: Staples Press. 1956.

This book starts with several rules for the student. The first is " understand the terms ", the second " distinguish theory from empirical evidence, and learn to withhold judgment ". It draws its material from many sources—behaviourism, Gestalt psychology, and psychoanalysis, but these are presented as an amalgam rather than a disconnected series of discordant views. The book is divided into four sections. The first, " An Introduction to Basic Concepts " is a good presentation of basic psychological principles. The second part, " The Problems of Disordered Behaviour ", is a short description of neurotic and psychotic syndromes. The third section, " The Causes of Disordered Behaviour ", discusses genetical, constitutional, and social factors. " Theories and Treatment of Disordered Behaviour ", the fourth section, is perhaps the weakest because of over-simplification. Nevertheless, one feels less with this book than with most others on psycho-pathology written by psychologists, that the authors are purely theoreticians. The book is likely to be of value to young psychiatrists not specifically trained in psychology, as a presentation of basic psychological concepts. For them the description of psychiatric syndromes and treatment is inadequate, though they may be adequate for the clinical psychologist, for whom this book is especially intended. All, however, will benefit from the very excellent guides to further reading which are given at the end of each chapter.

The Neuroses in Clinical Practice. By Henry P. Laughlin. (Pp. xlii + 802. 87*s.* 6*d.*) London and Philadelphia: W. B. Saunders. 1956.

This expensive and beautifully produced volume is a product of what is generally known as American dynamic psychiatry, which might be abbreviated, on the author's own system, to " A.D.P." In contradistinction to non-dynamic psychiatrists, whom one should presumably call static psychiatrists, adherents of A.D.P. deprecate the use of drugs and physical methods of treatment, and recommend intensive psychotherapy almost invariably as the treatment of choice. It may therefore be thought rather anomalous that the major advances in treatment of recent years should have come from the static psychiatrists, whereas the dynamic psychiatrists seem to be standing very much where they were several decades ago.

The author's approach to drugs is conservative in the extreme. For instance, on the treatment of depression he writes: " In certain occasional, very selected cases of *mild* depression, the amphetamines and the barbiturates can sometimes play a useful adjunctive role." The treatment of choice is " intensive psychotherapy in experienced hands ". Electroconvulsive therapy is, indeed, discussed, but more with regard to its unconscious meaning and its effect on unconscious punitive internal forces, than to indications and contraindications. At times the dynamism becomes too swift for the British reader. Thus phantom limb is regarded as conversion hysteria, and fainting is " a primitive type of defensive reaction by which one completely surrenders or shuts off outside perception ".

The 14 chapters of the book are devoted to anxiety, phobic reactions, conversion reactions, dissociative reactions, depression, fatigue reactions, hypochondriasis, obsessive-compulsive reactions, and neuroses following trauma, with separate chapters for mental mechanisms involved. At the end of every chapter there is a fairly extensive American bibliography, and at the end of the book glossary and indexes. Owing to its one-sided approach, however, it is not likely that neurologists and psychiatrists in this country will find the book of much value. Unfortunately it cannot be taken as a sound guide to prevailing American views on A.D.P., as the author is somewhat unorthodox in making anxiety the basis of all neuroses.

On the Early Development of Mind. By Edward Glover. (Pp. 483; 6 figures. 45*s*.) London: Imago Publishing Co. 1956.

The studies of the psychoanalyst are difficult to correlate with what is known of the physiology of the brain, and yet their investigations into the earliest stages of mind development make an important contribution to the understanding of brain mechanisms. Cerebral physiology and character formation must be built up as an elaboration of the primitive reactions of the infant in which, for example, the mouth and anus play an important part. Psychoanalytical theory often assumes a language and complexity which seem fanciful, and yet if one turns aside from much of the verbiage and studies the stages of character and mind development as demonstrated by psychoanalysis, much of interest will energe. This book is written with more respect for scientific standards than is shown by most writers on this subject and includes much of interest to the student of brain function.

Psychology of Exceptional Children and Youth. Edited by William Cruickshank. (Pp. xiii + 594; 24 figures. 42*s*.) London: Staples Press. 1956.

The 10 authors of this book have made a special study of special groups of children. These include not only the handicapped but also the gifted children. The last-named study is of particular interest to educationalists and others interested in mental development.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

The Primary Psychiatric Syndromes. By Dwight L. Moody. (Pp. xiv + 356. 37*s*. 6*d*.) Bristol: John Wright. 1956.

Neurology and Psychiatry in Childhood. Proceedings of the Association for Research in Nervous and Mental Disease, Vol. XXXIV. (Pp. xiii + 504; 63 figures, 21 tables. 88*s*.) London: Baillière, Tindall & Cox. 1954.

Expert Committee on Psychiatric Nursing. First Report. World Health Organization Technical Report Series No. 105. (Pp. 43. 1*s*. 9*d*.) London: H.M. Stationery Office; Geneva: World Health Organization. 1956.

Subarachnoid Haemorrhage. By John N. Walton; Foreword by Sir Charles Symonds. (Pp. xv + 350; 25 figures. 30*s*.) Edinburgh and London: E. & S. Livingstone. 1956.

The Neurosurgical Alleviation of Parkinsonism. By Irving S. Cooper. (Pp. xii + 104; 68 figures. 63*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1956.

Physiology of the Ocular and Cerebrospinal Fluids. By Hugh Davson. (Pp. viii + 388; 119 figures. 65*s*.) London: J. & A. Churchill. 1956.

Progress in Neurobiology: I. Neurochemistry. Edited by Saul R. Korey and John I. Nurnberger, with 23 contributors; Foreword by H. Houston Merritt. (Pp. 244; 29 figures, 41 tables. 50*s*.) London: Cassell. 1956.

Wisconsin Studies in Medical History No. 1: Franz Joseph Gall, Inventor of Phrenology and His Collection. By Erwin H. Ackerknecht and Henri V. Vallois; translated from the French by Claire St. Léon. (Pp. 86; 7 figures. $1.50.) Madison: The University of Wisconsin Medical School. 1956.

Nonverbal Communication: Notes on the Visual Perception of Human Relations. By Jurgen Ruesch and Weldon Kees. (Pp. 205; 78 figures. 56*s*. 6*d*.) London: Cambridge University Press. 1956.

Emotional Hazards in Animals and Man. By Howard S. Liddell. (Pp. xi + 97. 20*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1956.

An Introduction to Cybernetics. By W. Ross Ashby. (Pp. ix + 295. 36*s*.) London: Chapman & Hall. 1956.

Tredgold's Text-book of Mental Deficiency. Ninth edition by R. F. Tredgold and K. Soddy. (Pp. xvi+480; 31 plates, 4 figures, 4 tables. 40*s*.) London: Baillière, Tindall & Cox. 1956.

Mental Disorders in Later Life, 2nd ed. Edited by Oscar J. Kaplan. (Pp. ix + 508; 23 figures, 31 tables. 50*s*.) Stanford University Press (London: Cumberlege). 1956.

INDEX TO VOLUME 19, 1956

A

Addison's desease, clinical correlation between encephalopathy and papilloedema, in, 21
Affect, inappropriate, 308
Agnosia, visual, sensory defects in, 297
Anaemia, megaloblastic, ischaemic and postischaemic paraesthesiae in, 286
ANSELL, B. M., and CLARKE, E.: Disseminated sclerosis treated with isoniazid with a method of evaluating chronic neurological disorders, 144
Arteriography, cerebral, pathological effects of, 217
Ataxia, familial, association of familial peroneal muscular atrophy with, 155
———, hereditary, retinal degeneration in, 186
AUERBACH, I., *see* HOENIG, J., LEIBERMAN, D. M., and AUERBACH, I.

B

BARBER, C. R., and HEWITT, D.: Growth of skull in young children, II., 54
———, *see also* WESTROPP, C. K., and BARBER, C. R.
BEDFORD, P. D., and JAMES, F. E.: Family with progressive hypertrophic polyneuritis of Dejerine and Sottas, 46
Behaviour, sodium amytal and, in neurotic subjects, 137
BJÖRK, A., LINDBLOM, U., and WADENSTEN, L. Retinal degeneration in hereditary ataxia, 186
Bladder filling, awareness of, with divided sensory tract, 101

Books Received:

ACKERKNECHT, E. H., and VALLOIS, H. V.: Franz Joseph Gall, 1956, 317
Acta neurochirurgica, Supp. 3, 1955, 162
AMERICAN FOUNDATION.: Medical research, 1956, 240
ASHBY, W. R.: An introduction to cybernetics, 1956, 317
A.R.N.M.D.: Neurology and psychiatry in childhood, 1954, 317
BAKAY, L.: The blood-brain barrier, 1956, 239
BAKER, A. B., *ed.*: Clinical neurology, 3 vols., 1955, 162
BALINT. E.: Child psychology, 1956, 66
BECHER, H., *et al.*: Auge und Zwischenhirn, 1955, 66
BENDER, L.: Psychopathology of children with organic brain disorders, 1956, 240
BRADLEY, K. C.: Sequelae of amputation, 240
BRAGE, D.: Diencéfaloschock, 1956, 162
BROCHER, J. E. W.: Die Occipito-Cervical-Gegend, 1955, 162
CHAUCHARD, P.: Les mécanismes cérébraux de la prise de conscience, 1956, 240
Clinical neurosurgery, Vol. 2, 1955, 162
Contributi del Laboratorio di Psicologia, Vols. 48 and 49, 1955, 66
COOPER, I. S.: The neurosurgical alleviation of Parkinsonism, 1956, 317
DAVSON, H.: Physiology of the ocular and cerebrospinal fluids, 1956, 317
FIELDS, W. S., *et al.*, *eds.*: Hypothalamic-hypophysical interrelationships, 1956, 240
HARRIS, G. W.: Neural control of pituitary gland, 1955, 66
HEILMEYER, L.: Vorträge aus dem Gebiet der klinischen Chemie und Cardiologie, 1956, 162
HINDERMEYER, J.: Balance muscular, 1955, 66
KAPLAN, O. J.: Mental disorders in later life, 2nd ed., 1956, 317
KOREY, S. R., and NURNBERGER, J. I., *eds.* Progress in neurobiology, I., 1956, 317
LIDDELL, H. S.: Emotional hazards in animals and man, 1956, 317
MANSUY, L., and LECUIRE, J.: Les traumatismes cranio-cérébraux fermés récents, 1955, 66
Mental Health, May 1956, 239
MOODY, D. L.: The primary psychiatric syndromes, 1956, 317
NOBILI, C. C., and CERQUETELLI, G.: Gli sviluppi psicopatici, 1955, 66
PAILLAS, J., and CHRISTOPHE, L.: Les thromboses de la carotide interne et des ses branches, 1955, 66
POSER, C. M.: The relationship between syringomyelia and neoplasm, 1956, 239
RUESCH, J., and KEES, W.: Nonverbal communication, 1956, 317
Tredgold's Text-book of mental deficiency, 9th ed., 1956, 317
TROSTDORF, E.: Die Kausalgie, 1956, 162
WALTON, J. N.: Subarachnoid haemorrhage, 1956, 317
WOODGER, J. H.: Physics, psychology and medicine, 1956, 240
W.H.O.: Expert Committee on Psychiatric Nursing. First Report, 1956, 317

Book Reviews:

Acta neuropsiquiatrica argentina, Vol. 1, no. 1, 162
ALAJOUANINE, P. T.: Les grandes activités du lobe temporal, 1955, 236

ALDRICH, C. K.: Psychiatry for family physician, 1955, 237
BASH, K. W.: Lehrbuch der allgemeinen Psychopathologie, 1955, 237
BLEULER, M.: Endokrinologische Psychiatrie, 1954, 65
BRAIN, Sir R.: Diseases of nervous system, 5th edit., 1955, 236
BRAIN, Sir R., and STRAUSS, E. B.: Recent advances in neurology, 6th edit., 1955, 161
BROWER, D., and ABT, L. E., *eds.*: Progress in clinical psychology, Vol. II, 1956, 316
BUES, E. E.: Formen des posttraumatischen Kopfschmerzes, 1956, 236
CALLEWAERT, H.: Graphologie et physiologie de l'écriture, 1954, 162
CRITCHLEY, M.: James Parkinson, 1955, 238
CRUICKSHANK, W., *ed.*: Psychology of exceptional children and youth, 1956, 317
CURRAN, D., and PARTRIDGE, M.: Psychological medicine, 4th edit., 1955, 238
DAVIDOFF, L. M., and FEIRING, E. H.: Practical neurology, 1955, 316
DAVIES, N. C., and ENGLE, B., *ed.*: Wartime psychiatry, 1954, 162
DERBES, V. J., and KERR, A., *jr.*: Cough syncope, 1955, 161
ELLIOTT, K. A. C., *et al.*, eds.: Neurochemistry, 1955, 65
FAUST, C.: Die zerebralen Herdstörungen bie Hinterhauptsverletzungen und ihre Beurteilung, 1955, 236
FREUD, S.: Interpretation of dreams, 1955, 238
GLOVER, E.: On the early development of mind, 1956, 317
GREENFIELD, J. G.: The spino-cerebellar degenerations, 1954, 314
GUILLAIN, G.: J.-M. Charcot-sa vie- son oeuvre, 1955, 238
HALL, C. S.: Primer of Freudian psychology, 1956, 316
HEMERY, H. V.: Stammer is not nerves, 1955, 161
HESS, W. R.: Hypothalamus und Thalamus, 1956, 314
HILL, L. B.: Psychotherapeutic intervention in schizophrenia, 1955, 66
INSTITUTO NACIONAL DE ONCOLOGIA.: Tumores intracraneales, 1955, 314
JERSILD, A. T.: Child psychology, 4th edit., 1955, 238
KAHN, E. A., *et al.*: Correlative neurosurgery, 1955, 315
KATZENSTEIN, E.: Das Schädelhirntrauma, 1955, 314
KING, H. E.: Psychomotor aspects of mental diseases, 1955, 237
KOLLE, K., *ed.*: Grossen Nervenärzte, 1956, 238
LAUGHLIN, H. P.: The neuroses in clinical practice, 1956, 316
LAZORTHES, G.: Le système nerveux périphérique, 1955, 161
LUBARSCH, O., HENKE, F., and RÖSSLE, R., *eds.*: Handbuch der speziellen pathologischen Anatomie, Part IV, 1956, 314
MCILWAIN, H.: Biochemistry and the central nervous system, 1955, 239
MARSHALL, J.: Neurological nursing, 1956, 316
MITCHELL, G. A. G.: Cardiovascular innervation, 1956, 315
OBER, F. R.: Backache, 1955, 162
O'KELLY, L. I., and MUCKLER, F. A.: Introduction to psychopathology, 2nd edit., 1956, 316
O'NEILL, D., *ed.*: Modern trends in psychosomatic medicine, 1955, 161
PARKER, H. L.: Clinical studies in neurology, 1956, 316
PAVLOV, I. P.: Selected works, 1956, 239
PODOLSKY, E., *ed.*: Management of addictions, 1955, 239
PRICK, J. J. G., *et al.*: Thallium poisoning, 1955, 239
REHWALD, E., *ed.*: Das Hirntrauma, 1956, 314
RUSSELL, W. R.: Poliomyelitis, 2nd edit., 1956, 315
SAINSBURY, P.: Suicide in London, 1955, 239
SCHNEIDER, K.: Klinische Psychopathologie, 1955, 236
SCHULTZ, J. H.: Grundfragen der Neurosenlehre, 1955, 237
SHEDLOVSKY, T., *ed.*: Electrochemistry in biology and medicine, 1955, 239
SHOLL, D. A.: The organization of the cerebral cortex, 1956, 315
STALLWORTHY, K. R.: Manual of psychiatry, 3rd edit., 1955, 238
STANTON, A. H., and SCHWARTZ, M. S.: The mental hospital, 1954, 65
SULLIVAN, H. S.: Conceptions of modern psychiatry, 2nd edit., 1955, 237
SULLIVAN, H. S.: The interpersonal theory of psychiatry, 1955, 237
VALENTINE, M.: Introduction to psychiatry, 1955, 66
WALLIS, H. R. E.: Masked epilepsy, 1956, 315
WINDLE, W. F., *ed.*: Regeneration in the central nervous system, 1955, 315
Work of the mental nurse, 1955, 66
W. H. O.: The hospitalization of mental patients, 1955, 66

BRADSHAW, P.: Benign intracranial hypertension, 28
Brain, arteriography, pathological effects of, 217
——, benign intracranial hypertension, 28
——, blood vessels, prolonged and distant effects of brain injury on, as demonstrated by radioactive indicators, 202
——, cerebral dominance, paroxysmal dysphasia and problem of, 194
——, hamartomas of, cryptic arteriovenous and venous, 1
——, injury, experimental, prolonged and distant effects of, on cerebral blood vessels as demonstrated by radioactive indicators, 202
——, pearly tumours in relation to, 241

Brain, phosphatases of, action of, on lipid phosphate esters, 12
BRIERLEY, J. B.: Prolonged and distant effects of cerebral blood vessels as demonstrated by radioactive indicators, 202

C

CAMPBELL, A. M. G., and GARLAND, H.: Subacute myoclonic spinal neuronitis, 268
Carpal tunnel syndrome, electrical signs in diagnosis of, 275
Cauda equina, compression by prolapsed intervertebral discs, 109
Cerebellar pearly tumours, 251
Cerebello-pontine angle, pearly tumours in, 249
Cerebral arteriography, pathological effects of, 217
——— blood vessels, prolonged and distant effects of experimental brain injury on, as demonstrated by radioactive indicators, 202
——— dominance, paroxysmal dysphasia and problem of, 194
Chlorpromazine in chronic schizophrenia, controlled clinical study of, 232
CLARKE, E., *see* ANSELL, B. M., and CLARKE, E.
CRAWFORD, J. V., and RUSSELL, D. S.: Cryptic arteriovenous and venous hamartomas of brain, 1
CRAWFORD, T.: Pathological effects of cerebral arteriography, 217

D

Dejerine and Sottas, progressive hypertrophic polyneuritis of, family with, 46
Dementia, severe, following head injury, diffuse degeneration of cerebral white matter in, 163
Diploic pearly tumours, 246
Discs, intervertebral, prolapsed, compression of cauda equina by, 109
Disseminated sclerosis treated with isoniazid, 144
Dysphasia, paroxysmal, and problem of cerebral dominance, 194

E

Electro-convulsion therapy and insulin coma, effect on short-term prognosis of schizophrenia, 130
Electroencephalographic abnormalities from temporal lobe studied with sphenoidal electrodes, 117
Electrophoresis of sera in multiple sclerosis and other neurological diseases, 222
Electroplexy and hypoglycaemic therapies, altered response to small doses of insulin associated with, 57
Encephalomalacia, multilocular, 209
Encephalopathy and papilloederna, clinical correlation between, in Addison's disease, 21
ETTLINGER, G.: Sensory defects in visual agnosia, 297

F

Formalin, tissue stored in, for prolonged periods, value of Marchi method for staining, 62
FRANKS, C. M., *see* LAVERTY, S. G., and FRANKS, C. M.

G

GARLAND, H., *see* CAMPBELL, A. M. G., and GARLAND, H.
GESCHWIND, N., *see* WALTON, J. N., GESCHWIND, N., and SIMPSON, J. A.

H

Hamartomas of brain, cryptic arteriovenous and venous, 1
HARRIS, A., and METCALFE, M.: Inappropriate affect, 308
Head circumference, standards of, 52
——injury, severe dementia following, diffuse degeneration of cerebral white matter in, 163
——shape, changes in, 54
HÉCAEN, H., and PIERCY, M.: Paroxysmal dysphasia and problem of cerebral dominance, 194
HEMPHILL, R. E., *see* SMITH, S., and HEMPHILL, R. E.
HEWITT, D., *see* BARBER, C. R., and HEWITT, D.
HIERONS, R.: Familial peroneal muscular atrophy and its association with familial ataxias and tremor and longevity, 155
HOENIG, J., LEIBERMAN, D. M., and AUERBACH, I.: Effect of insulin coma and E. C. T. on short-term prognosis of schizophrenia, 130
Holmes-Adie syndrome, pupillary changes in, 289
Hydrocephalus, effect of duration of vitamin A deficiency in female rabbits on incidence of, in their young, 17
Hyperostosis frontalis interna, 42
Hypertension, intracranial, benign, 28
Hypoglycaemic therapies and electroplexy, altered response to small doses of insulin associated with, 57

I

Insulin, altered response to small doses of, associated with electroplexy and hypoglycaemic therapies, 57
——— coma and E. C. T., effect on short-term prognosis of schizophrenia, 130
Intervertebral discs, prolapsed, compression of cauda equina by, 109
Intracranial hypertension, benign, 28
Isoniazid in treatment of disseminated sclerosis, 144

J

JAMES, F. E., *see* BEDFORD, P. D., and JAMES, F. E.
JEFFERSON, A.: Clinical correlation between encephalopathy and papilloedema in Addison's disease, 21
JENNETT, W. B.: Study of 25 cases of compression of cauda equina by prolapsed intervertebral discs, 109

K

KERRIDGE, J., *see* PAMPIGLIONE, G., and KERRIDGE, J.
KRAMER, W.: Multilocular encephalomalacia, 209

L

LAVERTY, S. G., and FRANKS, C. M.: Sodium amytal and behaviour in neurotic subjects, 137
LEIBERMAN, D. M., *see* HOENIG, J., LEIBERMAN, D. M., and AUERBACH, I.
LINDBLOM, U., *see* BJÖRK, A., LINDBLOM, U., and WADENSTEN, L.
Lipid phosphate esters, action of phosphatases of brain on, 12
Longevity, association of familial peroneal muscular atrophy with, 155

M

Marchi method, artefacts of, recognition and prevention of, 74
——— ———, extended use of, 67
——— ———, for staining tissue stored in formalin for prolonged periods, value of, 62
MARLEY, E.: Altered response to small doses of insulin associated with electroplexy and hypoglycaemic therapies, 57
MARSHALL, J.: Studies in sensation: observations on localization of sensation of touch and prick, 84
——— and WALSH, E. G.: Physiological tremor, 260
MILLEN, J. W., and WOOLLAM, D. H. M.: Effect of duration of vitamin A deficiency in female rabbits upon incidence of hydrocephalus in their young, 17
Myoclonic neuronitis, acute spinal, 268
Myopathy, benign congenital, with myasthenic features, 224
——— limited to quadriceps; two cases, 106

N

NATHAN, P. W. Awareness of bladder filling with divided sensory tract, 101
——— Reference of sensation at spinal level, 88
Nervous system, central, pearly tumours in relation to, 241
Neurological disease, electrophoresis of sera in, 222
——— disorders, chronic, method of evaluating, 144
Neuronitis, myoclonic, acute spinal, 268

O

Orbit, pearly tumours, 243

P

PAMPIGLIONE, G., and KERRIDGE, J.: E. E. G. abnormalities from temporal lobe studies with sphenoidal electrodes, 117
Papilloedema and encephalopathy, clinical correlation between, in Addison's disease, 21
Paraesthesiae, ischaemic and postischaemic, 148
——— ——— — ———, in polyneuritis, 281
PENNYBACKER, J., *see* TYTUS, J. S., and PENNYBACKER, J.
Peroneal muscular atrophy, familial, and its association with familial ataxias and tremor and longevity, 155
Petrous pearly tumours, 244
Phosphatases of brain, action of, on lipid phosphate esters, 12
PIERCY, M., *see* HÉCAEN, H., and PIERCY, M.
Polyneuritis, ischaemic and postischaemic paraesthesiae in, 281
———, progressive hypertrophic, of Dejerine and Sottas, family with, 46
POOLE, E. W.: Ischaemic and postischaemic paraesthesia, 148
——— Ischaemic and postischaemic paraesthesia in polyneuritis, 148
PRESS, E. M.: Electrophoresis of sera in multiple sclerosis and other neurological diseases, 222
Pupil, changes in Holmes-Adie syndrome, 289

Q

Quadriceps, myopathy limited to, two cases, 106

R

Reserpine in chronic schizophrenia, controlled clinical study of, 232
Retina, degeneration of, in hereditary ataxia, 186
RUSSELL, D. S., *see* CRAWFORD, J. V., and RUSSELL, D. S.
RUSSELL, G. F. M.: Pupillary changes in Holmes-Adie syndrome, 289

S

Schizophrenia, chronic, controlled clinical study of chlorpromazine and reserpine in, 232
———, short-term prognosis of effect of insulin coma and E. C. T. on, 130
Sclerosis, disseminated, electrophoresis of sera in, 222
———, ———, treated with isoniazid, 144
Sensation of touch and prick, localization of, 84
———, reference of, at spinal level, 88
Sera, electrophoresis of, in multiple sclerosis and other neurological diseases, 222
SHARP, P., *see* SMITH, M. C., STRICH, S. J., and SHARP, P.
SHEPHERD, M., and WATT, D. C.: Controlled clinical study of chlorpromazine and reserpine in chronic schizophrenia, 232
SIMPSON, J. A.: Electrical signs in diagnosis of carpal tunnel and related syndromes, 275
——— *see also* WALTON, J. N., GESCHWIND, N., and SIMPSON, J. A.
Skull, growth of, in young children, Part I, Standards of head circumference, 52, Part II, Changes in head shape, 54
——, pearly tumours, 242

SMITH, M. C.: Observations on extended use of Marchi method, 67
————: Recognition and prevention of artefacts of Marchi method, 74
————, STRICH, S. J., and SHARP, P.: Value of Marchi method for staining tissue stored in formalin for prolonged periods, 62
SMITH, S., and HEMPHILL, R. E.: Hyperostosis frontalis interna, 42
Sodium amytal and behaviour in neurotic subjects, 137
Spinal canal, pearly tumours in, 255
—— neuronitis, subacute myoclonic, 268
STRICH, S. J.: Diffuse degeneration of cerebral white matter in severe dementia following head injury, 163
————, *see also* SMITH, M. C., STRICH, S. J., and SHARP, P.
STRICKLAND, K. P., THOMPSON, R. H. S., and WEBSTER, G. R.: Action of phosphatases of human brain on lipid phosphate esters, 12
Suprasellar pearly tumours, 247

T

THOMPSON, R. H. S., *see* STRICKLAND, K. P., THOMPSON, R. H. S., and WEBSTER, G. R.
Tissue stored in formalin for prolonged periods, value of Marchi method for staining, 62
Touch and prick, localization of sensation of, 84
Tremor, association of familial peroneal muscular atrophy with, 155
———, physiological, 260
Tumours, pearly, in relation to central nervous system, 241
TYTUS, J. S., and PENNYBACKER, J.: Pearly tumours in relation to central nervous system, 241

V

Visual agnosia, sensory defects in, 297
Vitamin A deficiency in female rabbits, effect of duration of, upon incidence of hydrocephalus in their young, 17

W

WADENSTEN, L., *see* BJÖRK, A., LINDBLOM, U., and WADENSTEN, L.
WALSH, E. G., *see* MARSHALL, J., and WALSH, E. G.
WALTON, J. N.: Two cases of myopathy limited to quadriceps, 106
————, GESCHWIND, N., and SIMPSON, J. A.: Benign congenital myopathy with myasthenic features, 224
WATT, D. C., *see* SHEPHERD, M., and WATT, D. C.
WEBSTER, G. R., *see* STRICKLAND, K. P., THOMPSON, R. H. S., and WEBSTER, G. R.
WESTROPP, C. K., and BARBER, C. R.: Growth of skull in young children, Part I., 52
WOOLLAM, D. H. M., *see* MILLEN, J. W., and WOOLLAM, D. H. M.